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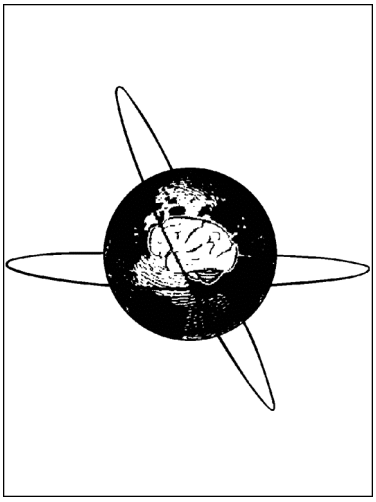

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Atypical brain activation in children who stutter in a visual Go/Nogo task: An ERP study

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Keywords:

Event related potential, Go/Nogo, children, stuttering, stimulus evaluation, inhibitory control.

Highlights

1. Children with stutter (CWS) show atypical brain activation compared to typically developing children (TDC) in a visual Go/Nogo task especially in the right frontal area.
2. CWS had prolonged N2 in both conditions while the Nogo P3 component was diminished compared to TDC.
3. Stimulus classification and/or inhibitory control may operate abnormally in the CWS.

Abstract

Objective: The aim of the study was to investigate inhibitory control by evaluating possible differences in the strength and distribution of the brain activity in a visual Go/Nogo task in children who stutter (CWS) compared to typically developing children (TDC).

Methods: Eleven CWS and 19 TDC participated. Event related potentials (ERP) were recorded using a 64-channel EEG-cap during an equiprobable visual Go/Nogo task. The global field power (GFP) as well as the mean amplitudes in the P3 time frame were compared between groups. Additionally, the potential maps of the groups were investigated visually in the N2 and P3 time windows.

Results: The groups differed significantly in the right frontal area especially in the Nogo condition ($p<.001$) with CWS showing smaller (less positive) mean amplitudes, most likely due to a prolonged and asymmetrical N2 component. Also the fronto-central Nogo P3 component was rather indistinct in CWS, but easily recognizable in TDC in the potential maps.

Conclusions: The CWS show atypical brain activation compared to the TDC in a Go/Nogo task as indexed by the excessive N2-related activity in both conditions and reduced P3-related activity in Nogo condition.

Significance: These findings indicate atypical stimulus evaluation and response inhibition processes in CWS.

1. Introduction

The ability to communicate is an essential part of our everyday lives and any problem in this area can have a harmful effect on the quality of life. In developmental stuttering, speech is characterized with repetitions, prolongations and blocks that make the speech dysfluent thus affecting communication negatively. According to current theories stuttering may arise from neurobiological and neurophysiological differences in brain areas 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 increasing number of studies have shown structural and 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 and Zhu, 2013). In an interesting study using magnetoencephalography (MEG), Salmelin et al. (2000) discovered a reversed sequence of activation in a delayed reading paradigm. Contrary to the fluent speakers, the left lateral central sulcus and dorsal premotor cortex were activated first and then followed by activation in the left inferior frontal cortex in the stutterers, indicating delayed articulatory programming versus motor preparation. The authors also suggested impaired functional connectivity between the left frontal cortex and the right motor/premotor cortex. Imaging studies have indicated decreased white matter integrity and thus reduced connectivity of left laryngeal and tongue representation areas in the sensorimotor cortex (Sommer et al., 2002), but also clusters of increased grey or white matter density in areas relevant to speech, for example the superior temporal gyri and especially the right primary auditory cortex (Beal et al., 2007). By using functional imaging Watkins et al. (Watkins et al., 2008) found over-activity bilaterally in the anterior insula, cerebellum and midbrain as well as the basal ganglia in persons who stutter when compared to fluent persons. On the other hand, persons with stuttering showed under-activity in areas essential for planning and execution of speech; bilateral ventral premotor cortex, Rolandic operculum, sensorimotor cortex and Heschl's gyrus on the left and in the premotor and motor cortices related to articulation and speech production. In addition, Watkins et al. found reduced white matter integrity in the detected under-active areas in the ventral premotor cortex.

Studies on children are scarce, but recently, Chang and Zhu (2013) showed that stuttering children aged 3-9 years had attenuated connections between both auditory-motor and cortical - basal ganglia areas on the left side compared to controls. Earlier Chang et al. (2008) found reduced grey matter volume (GMV) in left inferior frontal gyrus and bilateral temporal regions and reduced white matter integrity in the tracts below motor regions for face and larynx. Beal et al (2013) also found abnormalities in grey and white matter volume in CWS compared to fluently speaking children, more specifically reduced GMV in the bilateral inferior frontal gyri and left putamen, increased GMV in right Rolandic operculum and superior temporal gyrus and reduced white matter volume (WMV) bilaterally in the corpus callosum. These irregularities are only partially similar in stuttering children and adults implicating some plastic reorganization of the brain by age. Although more studies on young children are needed, these findings suggest reduced GMV and WMV mostly in the left hemisphere and decreased connectivity within left hemisphere or between hemispheres. Thus the over-activity or increased grey and white matter volume on the right might partially result from compensation of left-sided defects.

Also temperamental factors such as emotional reactivity have been proposed to affect the severity of stuttering (Conture et al., 2006; Bloodstein and Bernstein Ratner, 2008). These theories suggest that an intense reaction to a moment of dysfluency may increase speech disruption. However, questionnaires on temperament traits in CWS have not shown a higher level of anxiety or shyness (see review by Alm, 2014). Instead, some CWS showed traits typical of ADHD, such as inattention and impulsivity or hyperactivity. In recent studies using a questionnaire and a flanker task, the CWS showed poorer inhibitory control (Eggers et al., 2010) as well as atypical attentional orienting (Eggers et al., 2012), respectively. Inhibitory control is essential for attention and regulation of impulsivity. Basically it means the ability to prevent an inappropriate response when needed or, on the other hand, to perform a response when appropriate (Rothbart, 1989) or to ignore irrelevant information (Rothbart and Posner, 1985. Without sufficient inhibitory control, focusing on a complex task or processing information would be compromised.

The Go/Nogo paradigm is an inhibitory control related task. In this task the Go-signal requires a response, but to the Nogo-signal the response has to be withheld. In a recent study using the Go/Nogo subtest of the Amsterdam Neuropsychological Tasks (ANT) with equiprobable Go/Nogo stimuli, CWS

had more false alarms, premature responses and difficulties in adapting their response style after errors (Eggers et al., 2013) indicating abnormal inhibitory control in CWS. However, behavioral indices as errors and reaction time are quite robust measures and do not give detailed information on the underlying processes. For this reason, the Go/Nogo paradigm has commonly been combined with event-related potential (ERP) measurements in the study of inhibitory control (Johnstone et al., 2009; Johnstone et al., 2005; Jonkman, 2006; Jonkman et al., 2003; Piispala et al., 2016; Spronk et al., 2008). Compared to for example MRI, EEG- and ERP-measures have good temporal resolution and are therefore good methods to investigate fast cognitive processes.

In the Go/Nogo paradigm the negative N2 and positive P3 responses are the main ERP components modified by the paradigm. They are most distinguishable at 200-400 ms (N2) and 250-650 ms (P3) time windows depending on the stimulus and the paradigm (Jonkman et al., 2003, 2006; Johnstone et al., 2007). The N2 and P3 are both usually enhanced in the Nogo condition compared to the Go-condition (the Nogo effect) (Donkers and Van Boxtel, 2004; Falkenstein et al., 1999; Jonkman et al. 2003, 2006). In addition to the task parameters, age affects the ERPs (Brydges et al., 2013; Johnstone et al., 2005; also see review Huster et al. 2013). The Nogo effect on the N2 component is more distinct in children compared to adults. However, the Nogo P3 may be vague up to the age of 9 years (Johnstone et al., 2007; Jonkman, 2006; Spronk et al., 2008).

The N2 component is maximal fronto-centrally. It has been connected to inhibitory processes (Falkenstein et al., 1999; Pliszka et al., 2000) but also to conflict monitoring (Donkers and Van Boxtel, 2004; Enriquez-Geppert et al., 2010; Randall and Smith, 2011; Smith, 2011; see review by Van Veen and Carter, 2002) and novelty effect (Albert et al., 2013). The N2 component most likely consists of subcomponents that are activated differently when the task parameters are manipulated to increase either visual mismatch, conflict within the task or response inhibition demands, thus explaining the diverse results (Kropotov et al., 2011; for an overview, see also Folstein and Van Petten, 2008).

The P3 component has different topography in Go and Nogo conditions. Therefore the Go P3 and Nogo P3 components are probably produced by separate neural generators (Bokura et al., 2001; Gajewski and Falkenstein, 2011; Kropotov et al., 2011; Tekok-Kilic et al., 2001). The P3 seen in Go condition is maximal in centro-parietal regions both in adults (Barry and De Blasio, 2013; Bokura et al., 2001;

Tekok-Kilic et al., 2001) and children (Barry et al., 2014). It is believed to represent stimulus evaluation and classification similarly to the P3b in the oddball paradigm (Barry and Rushby, 2006; also see reviews by Polich, 2007 and Linden, 2005). The Nogo P3, on the other hand, is maximal fronto-centrally (Bokura et al., 2001; Tekok-Kilic et al., 2001; Johnstone et al. 2007; Jonkman, 2006; Smith, 2011). It may be specific to the inhibition process, as suggested by an increasing number of studies (Albert et al., 2013; Donkers and Van Boxtel, 2004; Smith et al., 2006; Smith et al., 2013).

Recently we performed a visual Go/Nogo task with simultaneous EEG-recording on 7-9 year old CWS and typically developed children (TDC) (Piispala et al., 2016). In this first Go/Nogo-ERP study on CWS we examined the N2 and P3 components in both Go and Nogo condition over 9 electrodes (F3,Fz,F4, C3,Cz,C4, P3,Pz,P4) along with behavioral measures. We found significantly delayed N2 component in the Go condition in CWS, indicating possibly atypical stimulus evaluation and/or response preparation. In contrast, there was no significant latency difference in the Nogo condition. No significant peak amplitude differences were seen for N2 or P3 components in either condition. Then again, the P3 peak was quite ambiguous and sometimes not even visible especially in the CWS, but the P3 latency seemed slightly delayed. In our study the groups did not differ significantly by errors or RT (see however Eggers et al., 2013).

Nevertheless, it is possible that the conventional approach using 9 centrally located electrodes may not have explored potential abnormalities thoroughly enough. Bearing in mind Eggers' findings (Eggers et al., 2013) and the reports of atypical temperament traits in CWS (for an overview, please see review by Alm, 2014), we hypothesize that the groups may allocate brain resources differently in the inhibitory task despite accurate performance in the behavioural task.

In addition to the GMV and WMV decrease seen in CWS (Beal et al., 2013; Chang et al., 2008; Chang and Zhu, 2013), hypo-activation is frequently seen in the left hemisphere in areas relevant to speech and language in PET and fMRI studies utilizing word or sentence reading or word repetition. This is often seen with simultaneous over-activation of right-sided areas such as right frontal operculum and pre-SMA (Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014; Chang et al., 2009; Preibisch et al., 2003). Also non-speech motor function has been abnormally lateralized in recent transcranial magnetic stimulation studies in adults who stutter (Alm et al., 2013; Neef et al., 2011; see also review

by Neef et al., 2015). Since the structural and functional aberrations in stuttering persons overlap structures relevant to inhibitory control (for an overview, see Chambers et al., 2009), the CWS could possibly show atypical lateralization of brain activity in an inhibitory task, as well. Also if the CWS need more effort to inhibit a response successfully, they may show a broader involvement of brain areas in the time window of the N2 and/or the P3 components. In that case we might see activity differences between wider brain regions or lobes instead of focally increased activation over a single electrode. Besides atypical spatial distribution, EEG activity might show abnormal temporal dispersion, resulting in delayed or prolonged ERP components overlapping or disfiguring later components.

Therefore, in order to recognize overall differences in brain activation in an inhibitory control task, we continued the analysis of the previously collected ERP data by calculating the global field power (GFP) over 60 channels and comparing them between the groups. The GFP is a measure of global brain activation calculated as the root mean-squared value of the EEG signal across all electrodes (Lehmann and Skrandies, 1980) and it represents the standard deviation of the momentary electrical field potential at the scalp. By using GFP waveforms it is possible to define a time frame where global activity is most diverse between groups. Due to the large variation of ERP waveforms across the scalp seen in the first analysis of the data (Piispala et al. 2016), the use of mean amplitudes instead of peak amplitudes or latencies seemed more appropriate, following the guidelines of the Society of Psychophysiological Research (Picton et al., 2000). Hence, in this study, the mean amplitudes around the maximal GFP difference were used for the statistical analysis. We focused particularly on the Nogo condition and the N2 and P3 time windows, because these components are most likely related to inhibitory control. In addition, we did visual topographic analysis of both conditions by using potential maps of all 64 channels. By using ERP-analysis in a visual Go/Nogo-task this study aims to further elucidate the aspects of brain function in CWS, especially the processes related to stimulus evaluation, response selection and inhibitory control.

2. Methods

2.1 Participants

The study group consisted of 11 CWS (age range 6.3-9.5 years; all right-handed boys) and 19 fluently speaking children (age range 5.8-9.6 years; 7 girls, one left-handed). The mean age was 8.1 years for both groups and there was no significant age difference between the groups (p=.966, Mann-Whitney U-test) as described in Piispala et al. (2016).

The parents did not report any health or developmental problems other than speech dysfluency in the stuttering group in a detailed written questionnaire. All children were screened for normal hearing (tone-audiometry, SA 50, Entomed, Sweden). The language production of the children was assessed by a qualified speech and language therapist from spontaneous speech samples and it was found normal.

Cognitive development of all the children was assessed by two subtests of Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991), Vocabulary and Block Design. These subtests were chosen because of their good correlation with the WISC-III overall score (Groth-Marnat, 2009). No significant between-group differences were found for either Vocabulary (p = .241, t-test) or Block Design (p = .573, t-test]. The mean scores for the Vocabulary subtests were 10 for the CWS (SD 3.9; range) and 12 (SD 3.5; range) for the TDC. In the Block Design subtest, the CWS scored on average 11 (SD 3.8; range) compared to 10 for the TDC (SD 3.6; range).

Prior to the study, participants and their parent(s) received information about the study .The parent(s) gave an informed, written consent and a verbal approval was obtained from the participants. The study was approved by the ethical committee of the Oulu University Hospital in accordance with the declaration of Helsinki.

2.2 Stimuli and procedure

The used visual Go/Nogo paradigm with 24 Go and 24 Nogo stimuli in one block has been described earlier (Piispala et al., 2016). The stimuli were presented in a pseudo-random order with a fixed inter-stimulus interval of 2800 ms. The Go stimulus was a green walking figure (as in traffic lights) and the

Nogo stimulus a red standing figure. Each stimulus was preceded by a small white cross that acted as fixation point and a non-informative cue. This cross was first visible for 500 ms then followed by the Go or Nogo stimulus for 800 ms.

During the task the child sat in a quiet, dimly lit room in front of a computer screen. For the Go stimulus, the child was instructed to press a special keyboard button and for the Nogo stimulus to do nothing. A correct Go response was a press within 300-3200 ms after the onset of the Go stimulus and a correct Nogo response was no press after a Nogo stimulus. All children practiced the task before the actual test. The child was monitored by a video camera. Between blocks short breaks were taken when necessary to maintain vigilance or for technical reasons. If the child was anxious, a parent was allowed to sit behind the child but instructed to stay quiet and still.

Continuous EEG was recorded throughout the task and correct and incorrect responses were measured, as well as reaction times (RT) for correct Go responses. In order to achieve enough acceptable segments for averaging of the event related potentials, children completed 4-6 blocks of 48 stimuli each.

2.3 EEG recording and analysis

For EEG recording we used Brain Products software and the BrainAmp DC amplifier with an electrocap (Acticap) with 64 Ag/AgCl electrodes. The sampling rate was 5000 Hz with resolution 0.1 μV and 0.016–1000 Hz on-line band pass. Two electrodes attached below or above the outer canthi of the left and right eyes, respectively, recorded eye movements. During the recording, the common reference was FCz, and after averaging the data were re-referenced off-line to the linked mastoids. Before ocular correction the data were digitally filtered off-line with a 0.01–40 Hz band pass filter and then with 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). For averaging, ERPs for correct Go and correct Nogo tasks were combined separately. Any epochs containing voltages ±125 μV were excluded.

2.4 Grand average and GFP waveforms

Grand average waves were formed from the individual waveforms for each group and condition and analyzed visually for defining the time windows for the N2 and P3 components as described in our earlier study (Piispala et al., 2016).

The global main field power (GFP) can be utilized instead of average latencies for identification of widely distributed peaks (Lehmann and Skrandies, 1980). The GFP was first computed to identify differences in global brain activation between the study groups. Global main field power was calculated as:

$$\mathrm{GMFP}(t) = \sqrt{\frac{\left[\sum_i^k (V_i(t) - V_{\mathrm{mean}}(t))^2\right]}{K}},$$

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 was calculated for each child in both conditions using 60 channels, leaving only the most lateral 4 electrodes out (FT9, FT10, PO9, PO10). Then the GFP difference wave between groups was computed separately for both conditions. The point of maximal GFP difference was used to define a 40 ms time window for the mean amplitude measurement.

2.5 Potential maps

For potential maps an 80 ms time window around the maximal difference in the GFP waves in Nogo condition was chosen, overlapping the N2 the P3 time windows seen in the grand average waves. Potential maps between 350 ms -510 ms were formed from the data using Brain Vision Analyzer software and its mapping view. The potential maps of each group and condition were visually assessed. For each condition, the scaling with the best visualization of the voltage differences across the scalp was chosen and used for both groups.

2.6. Statistical analysis

For the statistical analysis, 36 channels were used as the most lateral and occipital electrodes were discarded. After restructuring the data, 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). Since the data of each subject at different electrode locations are correlated, we chose a linear mixed model approach for the analysis. It was performed using the SPSS statistical analysis program ((IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) with Mean amplitude as the 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) as factors for fixed effects and subject ID as a factor for random effects.

The 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 Group-Region variable was then used as a factor for fixed effects in the mixed linear model. The Go and Nogo conditions were tested separately. Because of the low number of comparisons corrections were considered unnecessary (Rothman, K.J., 1990).

3. Results

3.1 Grand average and GFP analysis

The estimated time frame for the N2 component was 300-420 ms and 380-500 ms for the P3 component in the grand average figures (Piispala et al., 2016) (Fig 1). The GFP waveform showed a clear peak at around 350 ms, fitting the N2 time window. In the P3 time frame another, smaller peak was seen at 430 ms particularly in the TDC and in the Nogo condition (Fig 1).

[Figure 1]

The GFP difference wave between groups showed a small peak at 435 ms in Go (Fig 2 a) and a well-defined peak at 430 ms in Nogo condition in the P3 time frame (Fig 2 b). The mean amplitude of a 40 ms segment around the difference wave peaks (415-455 ms in Go and 410-450 ms in Nogo) was used in the statistical analysis to examine possible local differences.

[Figure 2 a]

[Figure 2 b]

3.2. Potential maps

Potential maps were used to visualize possible topographic differences between groups in the time window where the GFP waveforms differed between groups. Upon visual inspection of the potential maps the groups showed clear differences in the activity in the time window between 350-510 ms poststimulus (Fig 2 a and b, see also Supplementary Material).

In both conditions, a widely distributed and long lasting negatively oriented activity was found at around 350-440 ms in the CWS resulting in lower amplitudes. I contrast, in TDC this negative activation was frontally limited and much shorter in duration, vanishing already at 390 ms (Fig 2 a and b). In Go condition neither group showed any clear positivity in the fronto-central region in the P3 time frame, but in the parietal area there was positively oriented activity (Fig. 2 a). At around 400-450 ms post-stimulus in Nogo condition the TDC showed at around 400 – 450 ms poststimulus a distinct, almost symmetrical positivity at the fronto-central leads. In the CWS, however, this positively oriented activity was barely visible (Fig. 2 b).

3.3. Mean amplitude linear mixed model analysis

3.3.1. Between-group differences

In the Go condition the linear mixed model analysis revealed a significant main effect for Region ($p<.001$) between 415-455 ms. The main effect for Group was not significant ($p=.264$), but there was a significant Group x Region interaction ($p=.049$) (Table 1). Considering the small n in our study, these p-values likely support the alternative hypothesis of a significant difference between groups. The CWS showed smaller mean amplitudes than the TDC throughout all regions (Table 2), but the post-hoc analysis using the Group-Region variable as a factor in a linear mixed model analysis and comparing mean amplitudes of regions between groups showed that the main effect was due to the difference in the right frontal area ($p=.050$).

In the Nogo condition the mixed model analysis of the mean activity between 410-450 ms showed a significant main effect for Region ($p=.014$), but not for Group ($p=.180$). There was a highly significant Group x Region interaction ($p<.001$) (Table 1). Similarly to the Go condition, the mean amplitudes were higher in the TDC compared to CWS (Table 2). In the post-hoc analysis the difference between groups was significant in the Right Frontal region ($p=.041$). Furthermore, there was a slight, but not significant difference in the Right Central region ($p=.069$).

		Go	Nogo
Main effect	Group	.264	.180
	Region	<.001	.014
Interaction	Group x Region	.049	<.001
Pairwise comparisons between groups	Right frontal	.050	.041

Table 1. Summary table of the linear mixed model main effects and interactions and the between group comparison of the mean amplitudes of regions (between 415-455 ms time range in the Go

condition and in 410-450 ms in the Nogo condition). Only effects and comparisons with $p \leq .05$ are shown.

Region	Group	Go		Nogo	
		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

Table 2. Mean amplitudes of the regions in the 415-455 ms time range in the Go condition and 410-450 ms in the Nogo condition. 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).

3.3.2 Pairwise-comparisons within groups

In both conditions there were statistically significant inter-regional differences that were unalike in CWS and TDC, especially in the Nogo condition. In the Go condition and in both groups, the parietal regions showed the highest mean amplitudes (Table 2) and the midline frontal area the lowest. Both in the TDC and CWS all parietal areas differed significantly from all frontal and central areas. In the TDC, midline frontal region differed from the right frontal and central regions (Table 3). However, in the CWS also the amplitudes of the lateral frontal areas were smaller, when compared to the central areas, and both right and left frontal areas differed from lateral central areas contra- and ipsi-laterally.

In the Nogo condition in the TDC the midline central region showed the highest mean amplitude and the parietal regions the lowest mean amplitudes (Table 2). In TDC especially the left parietal region diverged significantly from all central and frontal areas, while there was no significant difference between frontal and central regions (Table 3). In contrast, in the CWS the maximal mean amplitude was in the midline parietal region and the smallest amplitude in the right frontal area. In CWS, the right frontal region differed significantly from all parietal regions as well as left central region (Table 3).

		Go		Nogo	
Region pairs		CWS	TDC	CWS	TDC
Left frontal	-left central	.012			
	-right central	.023			
Midline frontal	-right frontal		.038		
	-right central		.027		

Right frontal	-left central	.007		.002	
	-right central	.013			
Left parietal	-left frontal	<.001	<.001		<.001
	-midline frontal	<.001	<.001		.005
	-right frontal	<.001	<.001	.029	<.001
	-left central	<.001	<.001		<.001
	-midline central	.002	<.001		<.001
	-right central	<.001	<.001		<.001
	-right parietal				.003
Midline parietal	-left frontal	<.001	<.001		
	-midline frontal	<.001	<.001		
	-right frontal	<.001	.001	.012	
	-left central	<.001	<.001		
	-midline central	.002	.001		.005
	-right central	<.001	.001		.008
Right parietal	-left frontal	<.001	<.001		
	-midline frontal	<.001	<.001		
	-right frontal	<.001	<.001	.002	
	-left central	<.001	<.001		
	-midline central	.001	.002		.027
	-right central	<.001	<.001		

Table 3. Pairwise comparisons within groups.

Pairwise comparisons of the mean amplitudes between regions in the 415-455 ms time range in the Go condition and in 410-450 ms in the Nogo condition separately for the CWS and TDC. Only comparisons with significant differences ($p \leq .05$) are shown.

4. Discussion

The brain activity of the CWS differed from the TDC especially in the Nogo condition, confirming our hypothesis of atypical spatial and temporal distribution of inhibitory control related EEG activity in

CWS. The groups showed significant differences in the P3 time window as indexed by the amplitude as well as the distribution of the electrical field, with lower amplitudes in the right frontal area in the CWS when compared to the TDC.

4.1. The potential maps and ERPs

In the 350-430 time window in CWS and around 350-390 ms in TDC the potential maps showed negatively oriented activity in both conditions. This activity most likely produces the N2 component seen in the grand average figures given the polarity, time window and topography of the activity (Donkers and Van Boxtel, 2004; Enriquez-Geppert et al., 2010; Falkenstein et al., 1999; Pliszka et al., 2000; see review by Van Veen and Carter, 2002). In the CWS, this was widened, prolonged and asymmetrical compared to the TDC.

Then again, the fronto-central positivity clearly visible in TDC in the Nogo condition is consistent with the Nogo P3 in the literature by its topography and behavior in the task (Tekok-Kilic et al., 2001; Bokura et al., 2001; Jonkman, 2006; Johnstone et al., 2007). From the potential maps it seems clear, that the CWS show very little Nogo P3 activity compared to the TDC. In Go condition, neither group showed any clear positivity fronto-centrally in the P3 time window, but instead in the parietal areas, which is consistent with the literature of the Go P3 in adults (Barry and De Blasio, 2013; Tekok-Kilic et al., 2001; Bokura et al., 2001) and children (Barry et al., 2014).

The prolonged N2 negativity apparently partially overrides the P3 component in the CWS affecting the amplitude. However, mere delay of the N2 does not explain the difference in the figures as also the spatial distribution of activity seems divergent. The CWS have significantly smaller (less positive) amplitudes on the right frontal area, contrary to the TDC with symmetrical and altogether higher amplitudes frontally. Most likely the differences between groups in the Nogo condition are due to discrepancies in both the P3 and the N2 component; a delayed, asymmetrical and excessive N2 and a diminished P3 component in the CWS.

4.2. ERPs and inhibitory control

4.2.1 The N2 and P3 components in Nogo condition

One of our hypotheses was that the CWS need to recruit more resources to perform the task, which would be shown as excessive or widened brain activation. This seems to be the case here in the N2 time window. Most often the N2 component in inhibitory tasks is suggested to arise from the anterior cingulate cortex (ACC) (Jonkman et al., 2007; Niewenhuis et al., 2004; Van Veen and Carter, 2002; Bekker et al., 2005). ACC is involved in 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). Abnormal N2 activity as indicated by prolonged duration of the component could represent difficulties in the stimulus categorization (Gajewski et al., 2008) or response selection (Barry et al., 2014; and Barry and De Blasio, 2013) which in turn affects the sequential processing chain and the P3 component. On the other hand, increase of the N2 amplitude has been shown to correlate positively with successful inhibition in both stop-signal and Go/Nogo tasks (Johnstone et al., 2007; Falkenstein et al., 1999; Pliszka et al., 2000). In one study on ADHD (Smith et al., 2004), the Nogo effect on N2 was higher in children with ADHD, interpreted as the use of more effort in the inhibitory process. Similarly to our study, the behavioral results were similar between the clinical group and the controls. Thus it is plausible that the widened and prolonged N2 activity in CWS reflects compensatory mechanisms that enable adequate performance despite possible abnormality in stimulus processing and classification mechanisms.

However, due to the considerably reduced Nogo P3 component in CWS, we suspect also independent problems of later, perhaps more explicitly inhibition-related phases of the process. The P3 component in Nogo condition has been linked to inhibition by many studies (Donkers and Van Boxtel, 2004; Albert et al., 2013; Smith et al., 2006). In inhibitory tasks the P3 generators have usually been located in the right frontal lobe (Strik et al., 1998; Enriquez-Geppert et al., 2010; Kropotov et al., 2011), especially the inferior-frontal cortex and the supplementary motor cortex. However, associated activity has been seen in a wide frontal and fronto-parietal network on both hemispheres and even temporo-parietal regions in visual tasks (Jamadar et al., 2010; Steele et al, 2013; please see also review by Huster et al., 2013). By a recent study, the Nogo P3 was proposed to arise from motor deactivation related positivity that is associated with inhibition (Smith et al., 2013). Smith et al. conducted a

complex Go/Nogo task with either motor or silent count responses and recorded ERPs and fMRI during successful Nogo condition. The Nogo P3 was enhanced in the motor versus the non-motor inhibition task, although no response was required in either task. In contrast, in Go condition the P3 was similar in motor and count situations. According to the fMRI during the same task, the motor inhibition task was associated with deactivation of a network of motor related regions, more so on the left side. The authors proposed that the Nogo P3 in a motor inhibition task is a result of active motor suppression. The diminished or absent Nogo P3 in the CWS in our study could thus indicate atypical inhibitory mechanisms, possibly with inefficient motor deactivation when compared to the TDC.

4.2.2 The N2 in Go condition

In Go condition, the activity between groups differed in the right frontal areas. Similarly to the Nogo condition, the CWS showed the remnants of a delayed and prolonged N2 as indexed by more negative amplitudes in the frontal areas in the inspected time frame between 415-455 ms, while the TDC had already more positive activity at this time point. The N2 related activity seems slightly asymmetrical but also more intense in the CWS according to the potential maps. It may represent the need to allocate more resources in the stimulus classification and response selection process, resulting in a disproportionate N2-related activity, similarly to the Nogo condition. The prolonged N2 component in Go condition corroborates with the findings of our previous analysis as the increased duration of the N2-related activity in the CWS most likely resulted in a delayed peak latency of the N2 component (Piispala et al., 2016).

4.3 Atypical lateralization

The atypical distribution of brain activity in persons who stutter when compared to controls has been shown both in vocal tasks with fMRI or PET imaging (Please, see meta-analysis by Belyk et al, 2015 and Budde et al., 2014) as well as in non-speech motor studies using TMS (Alm et al., 2013; Neef et al. , 2011; see also review by Neef et al., 2015). Many recent studies have implied that the main problem lies in the connective white matter tracts of the brain rather than specific cortical areas. Both children (Chang et al., 2015) and adults who stutter (Cai, S. et al., 2014; Civier et al., 2015)

have shown reduced connectivity between auditory and motor areas mostly on the left side, as well as in the corpus callosum. Some of the structural and functional abnormalities found in CWS and AWS overlap areas involved in the Go/Nogo task and inhibition in general (Steele et al., 2013, for an overview, please see Chambers et al., 2009). Although the spatial accuracy of EEG-measurements is poor compared to for example MRI, our findings of atypical lateralization of brain activation in CWS in this visual, motor inhibitory control task are in agreement with the previously documented functional and structural differences.

The suspected spatial difference seen in CWS in our study could be due to many alternative or simultaneous mechanisms. The less positive amplitudes on the right frontal area in CWS may reflect a lack of motor deactivation that would normally generate a positive deflection in the ERP wave in the Nogo condition (Smith et al., 2013). This would correlate with the documented over-activation of motor areas on the right side in adults who stutter (Belyk et al.2015; Brown et al., 2005; Budde et al., 2014; Neef et al., 2015). This may be a compensatory means to overcome left-sided malfunctions in the motor control but perhaps also stimulus processing and inhibitory control. Decreased inhibitory regulation via corpus callosum may also activate right-sided structures abnormally, instead of beneficial compensation, as proposed by Civier et al. (Civier et al., 2015). Then again, decreased white matter connectivity in CWS (Chang et al., 2015) could lead to increased temporal dispersion of N2- and P3-related processes, as well, affecting the synchronization of activity between hemispheres and thus the duration of ERP components.

5. Caveats and confounds

In our previous analysis we could not detect any significant amplitude differences either in Go and Nogo condition, which seems contradictory to our current results. However, the comparisons using only 9 electrodes and N2 peak amplitudes were not significant most likely because of the widened distribution and duration of the N2 activity in CWS. Then again the P3 peaks were difficult to define in the ERP-waves of the CWS. The peak latency and amplitude comparisons were therefore problematic, leading us to continue and extend the analysis of the data, as presented here. In the light of our

findings in the re-analysis, the diminished or lacking Nogo P3 component in CWS seems a true phenomenon.

In our study we averaged more than 77 trials per child for each condition, thus minimizing the effect of coincidental errors on the ERP waveform. Also the use of 64 channels increases spatial accuracy of the study, compared to frequently used electrode settings with 19 or 32 channels. However, although the scalp distribution shows a spatial difference, the location of actual neural generators may not differ as clearly, due to confounding effect of the source strength (McCarthy and Wood, 1985). We thus recognize that the neural generators and exact cognitive processes that create the ERP-abnormalities cannot be conclusively determined by this experiment. In order to determine the possible structural differences behind the ERP-findings the combination of other techniques, such as fMRI or MEG, would be necessary.

The CWS form a heterogeneous group with possibly different etiologies, brain abnormalities and coping strategies, which may produce very dissimilar brain activations (Wymbs et al., 2013). Individual ERP-waveforms showed large variation especially in the CWS, which also affected the analysis of the peaks in our previous study. Further studies using various paradigms are needed to clarify the concept of inhibitory control and compensatory activity in CWS.

6. Conclusion

There is a marked difference in brain activity between CWS and TDC especially in the Nogo condition of the Go/Nogo task. The CWS showed a weak or absent Nogo P3 component compared to TDC supporting the hypothesis of atypical inhibitory control, possibly through inefficient deactivation of motor areas. Both in Go and Nogo conditions the preceding N2 component was widened and prolonged in the CWS, affecting especially the right frontal areas. This may be a compensatory mechanism due to altered stimulus categorization or response selection processes that complicate also the inhibition process in the CWS. These results indicate that the atypicalities of the cognitive processes in the CWS compared to fluently speaking children extend beyond speech or auditory tasks or pure motor performance. In this case CWS might benefit from implementing neuropsychological rehabilitation methods along with traditional speech therapy in a multi-disciplinary fashion. Also when knowledge of

the underlying pathology and the accompanying plastic changes grows, other therapeutic measures may emerge, for example repetitive transcranial magnetic stimulation (rTMS) in treatment of stuttering.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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Figure Legends

Figure 1. The grand average (GA) and global field power (GFP, note the polarity) waveforms in the Go and Nogo conditions.

The time windows between 415-455 ms and 410-450 ms in the Go and Nogo condition, respectively, are highlighted. The GA waveforms of the typically developed children (TDC) showed a precise P3 peak especially in the Nogo condition, but for the children who stutter (CWS) it is less clear. The global field power (GFP) is a computed measure of the EEG-activity across all electrodes (Lehmann and Skrandies, 1980). It represents the standard deviation of the momentary electrical field potential at the scalp and is always positive in value. The GFP and ERP peaks are temporally related, as the electrical field shows greater deviation at the time of the focal ERP peak maxima. The GFP waveform of the TDC shows a small peak in the P3 time window in the Nogo condition, contrary to the CWS.

Figure 2 a. 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 figure only presents the potential maps at time points every 15 ms between 350-395 ms (top left rows) and 465-510 ms (bottom right rows). However, for the most interesting 40 ms segment around the maximal GFP difference, between 415-455 ms (middle rows), potential maps represent time points every 10 ms. In Go condition the CWS show increased and prolonged negatively oriented activity when compared to the TDC.

Figure 2 b. The global field power (GFP) difference wave between children who stutter (CWS) and typically developed children (TDC) and their potential maps in the Nogo condition.

The potential maps represent time points every 15 ms between 350-395 ms (top left rows) and 465-510 ms (bottom right rows) and every 10 ms in the 40 ms time window around the maximal GFP difference, between 410-450 ms (middle rows). In this time frame, the CWS show very little fronto-central positively directed activity when compared to the TDC. In the CWS there is a prolonged negatively oriented activity in the frontal areas, whereas in the TDC it vanishes already at around 390 ms.

Figure 1

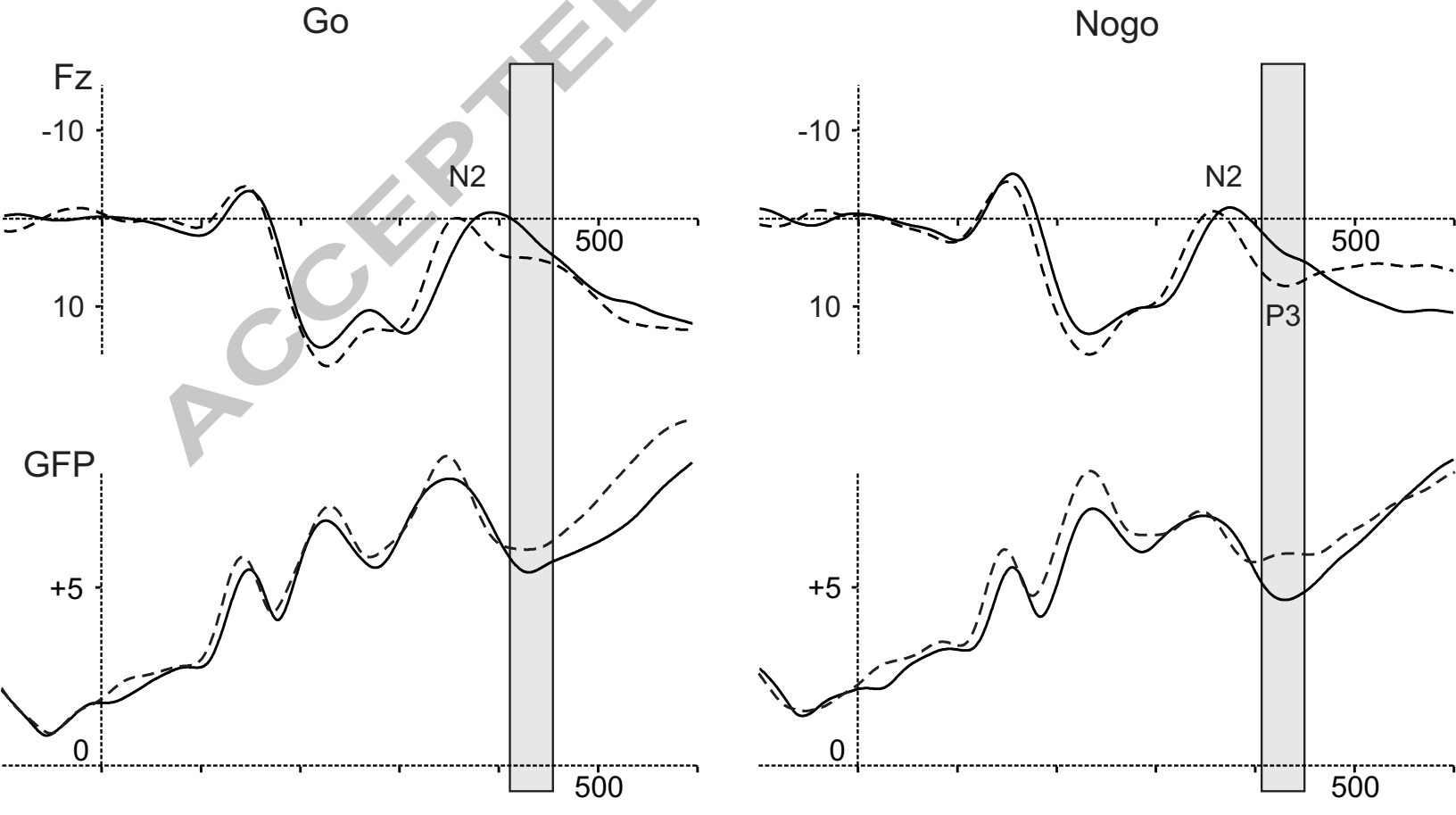

Figure 2a

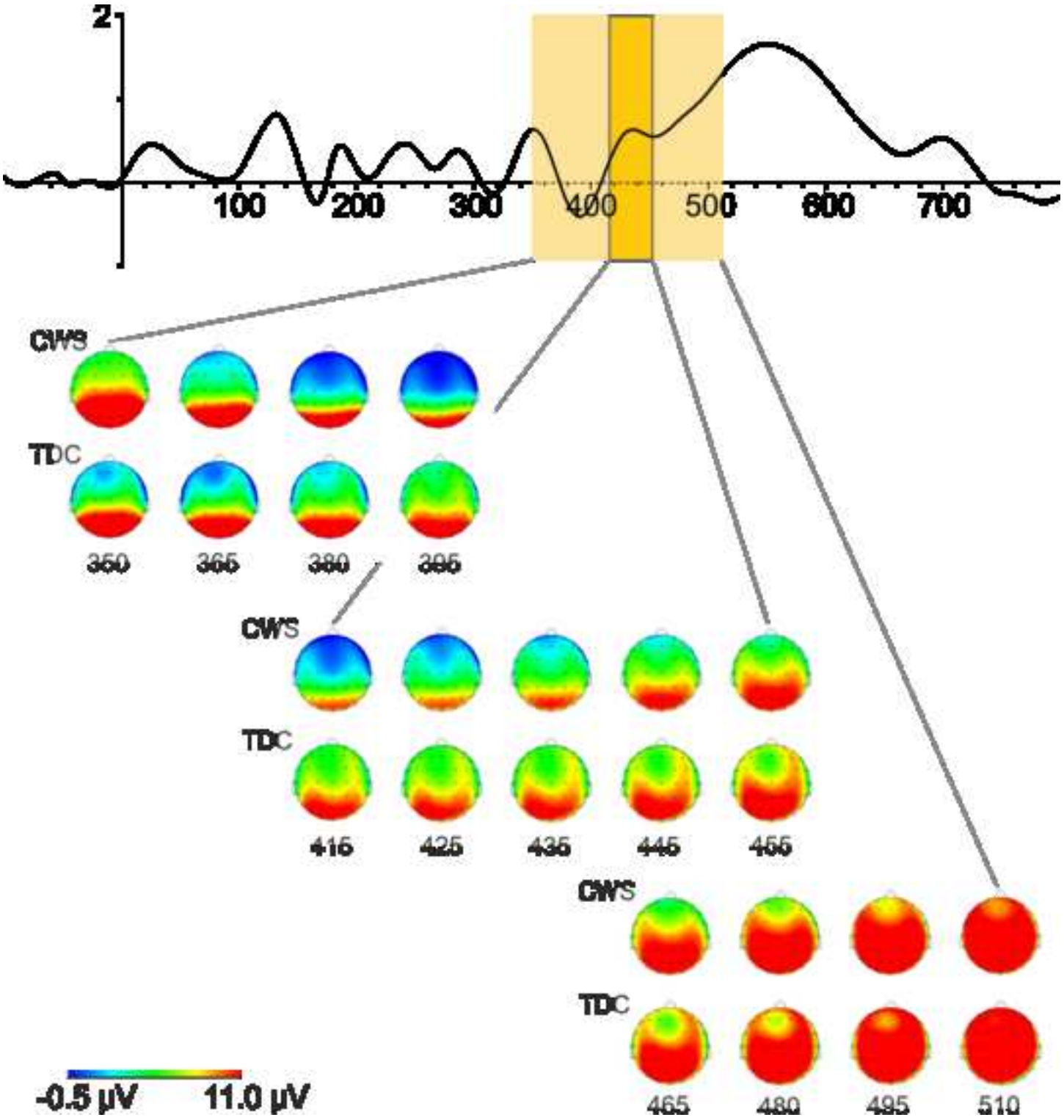

Figure 2b