# Separating Mismatch Negativity (MMN) Response from Auditory Obligatory Brain Responses in School-Aged Children

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## Abstract

Mismatch negativity (MMN) overlaps with other auditory event-related potential (ERP) components. We examined the ERPs of fifty 9-11-year-old children for vowels /i/, /y/ and equivalent complex tones. The goal was to separate MMN from obligatory ERP components using principal component analysis (PCA) and equal probability (EQ) control condition. In addition to the contrast of the deviant minus standard response, we employed the contrast of the deviant minus control response, to see whether the obligatory processing contributes to MMN in children. When looking for differences in speech deviant minus standard contrast MMN starts around 112 ms. However, when both contrasts are examined, MMN emerges for speech at 160 ms whereas for non-speech MMN is observed at 112 ms regardless of contrast. We argue that this discriminative response to speech stimuli at 112 ms is obligatory in nature rather than reflecting change detection processing.

*Keywords:* language/speech**,** children/infants, EEG/ERP, MMN, EQ paradigm, vowel

## Introduction

Pre-attentive detection of changes in the auditory environment is an important ability that has early evolutionary origins and is used, for example, in discriminating differences in speech streams. An electrophysiological index of auditory change detection is a brain event-related potential (ERP) called mismatch negativity (MMN). The process generating MMN has been proposed to be biologically significant and often leading to involuntary attention shift to variations in the environment (Csépe, 1995; Schröger, 1997; Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010). This change detection process is already discernible in infants (Leppänen, Eklund, & Lyytinen, 1997; Cheour et al., 1998a; Cheour et al., 1998b; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Cheour, Leppänen, & Kraus, 2000; Leppänen, Guttorm, Pihko, Takkinen, Eklund, & Lyytinen, 2004), which in part has resulted in its wide application as an index of auditory processing abilities when studying speech development and auditory / speech perception deficits in clinical populations (Näätänen, Paavilainen, Rinne, & Alho, 2007). During childhood ERPs typically show considerable changes in waveform morphology with emergence of N1-P2 complex and relative diminution of P1-N250 complex with age (Ponton, Eggermont, Kwong, & Don, 2000). These changes in obligatory responses occur at the same time window as MMN in children (Cheour et al., 2000; Gomot, Giard, Roux, Barthelemy, & Bruneau, 2000; Shafer, Morr, Kreuzer, & Kurtzberg, 2000; Shafer, Yu, & Datta, 2010). Therefore, it is important to examine how the variance related to each of these components can be dissociated from each other in children.

MMN is generated automatically and pre-attentively by infrequent deviations or changes in a constant stimulus train and it occurs to changes in several auditory features, e.g. frequency, duration and intensity (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen et al., 2007). In adults MMN peaks at 100–200 ms after the onset of the stimulus deviance with a distribution of fronto-central negativity and reversal of polarity into positivity at electrode sites below the Sylvian fissure (Näätänen, 1992; Näätänen et al., 2007). MMN is composed of at least temporal and frontal sources. The temporal source, generated bilaterally in the supratemporal plane of the auditory cortex, is thought to be related to sensory memory processing of the auditory features (Näätänen, et al., 1978; Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen, 1992), whereas the frontal source, usually with a right hemispheric dominance, is associated with automatic attention switching or a ‘contrast enhancing’ mechanism of sharpening the processing

of the incoming stimulus (Giard et al., 1990; Gomot et al., 2000; Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002; for a review, see Deouell, 2007).

Mismatch negativity is typically generated in an oddball condition where infrequent deviant stimuli are embedded among frequently occurring standard stimuli (Näätänen, 1992; Näätänen & Alho, 1997; Näätänen, Jacobsen, & Winkler, 2005). It is thought that MMN is elicited when a sensory input from the deviant stimulus does not match with the memory trace developed by the repeated standard stimulus. An alternative interpretation suggests that the deviant stimulus, instead of initiating a memory-based change-detection process, merely generates activation of new afferent neuronal populations resulting in a difference between the responses to the deviant and standard stimuli, and thus the detection of change (Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991; Näätänen, 1992; Jääskeläinen et al., 2004; Näätänen et al., 2005; May & Tiitinen, 2010). While there is a bulk of evidence for memory trace based explanation, a large difference between standard and deviant stimulus can also generate a difference between obligatory responses, for example in N1, which often overlaps with MMN (Näätänen & Picton, 1987; Näätänen et al., 2005).

In the course of maturation, response complex of auditory obligatory ERPs, P1-N1-P2-N2, undergo developmental changes in morphology, latency, and amplitude (Cunningham, Nicol, Zecker, & Kraus, 2000; Ponton et al., 2000). In general, the latencies of ERP components shorten with maturation, which is suggested to be due to increasing myelinisation and changes in synaptic density with age (Ponton et al., 2000; Moore & Guan, 2001). Auditory ERP is dominated by P1-N2 complex from infancy until early school-age, and at about 9 years of age an adult-like N1-P2 complex begins to emerge at fast stimulation rates (<1 s) to take the dominance by adulthood (Ponton et al., 2000; Kushnerenko et al., 2002; Ruhnau, Herrmann, Maess, & Schröger, 2011). Both P1-N2 and N1-P2 complexes are observed in adults (e.g. Čeponienė, Rinne, & Näätänen, 2002). Contrary to the other ERP components, several studies have shown MMN to be relatively stable during life time, being highly comparable with the adult response by early school-age (Čeponienė, Cheour, & Näätänen, 1998; Cheour, Leppänen, & Kraus, 2000; Cheour, Korpilahti, Martynova, & Lang, 2001; Hämäläinen, Leppänen, Guttorm, & Lyytinen, 2008; Hämäläinen, Ortiz-Mantilla, & Benasich, 2011).

Because of the relatively long latency ranges and long duration of auditory brain responses in children, MMN often overlaps with earlier obligatory ERP components (see Fig. 1, based on latencies in Ponton et al., 2000). This is especially true for N1 and particularly for its frontal and supratemporal sub-components (Näätänen & Picton,

1987; Bruneau & Gomot, 1998) and for N2 (or often referred to as N250 in children) which has fronto-central distribution (Čeponienė, Alku, Westerfield, Torki, & Townsend, 2005) and bilateral sources in the supratemporal auditory cortex (Bruneau & Gomot, 1998). N1 and N2 are difficult to separate from MMN response both temporally and spatially as they arise from similar brain areas and overlap in time. MMN-N1-overlap has been rather extensively studied in adults over the last decades (e.g., Schröger & Wolff, 1996; Jacobsen & Schröger, 2001; Jacobsen, Horenkamp, & Schröger, 2003; Jacobsen & Schröger, 2003; Campbell, Winkler, & Kujala, 2007; Schröger, 2007; Horváth, Czigler, Jacobsen, Maess, Schröger, & Winkler, 2008), but in children more information about the overlap is needed. Due to the overlap and given that the differences between the responses to standard and deviant stimuli can also be caused by other factors than change detection, for example, by physical stimulus difference and neuronal refractoriness discrepancy related to presentation probability (Walker et al., 2001), the identification of genuine mismatch negativity amongst the obligatory responses becomes challenging.

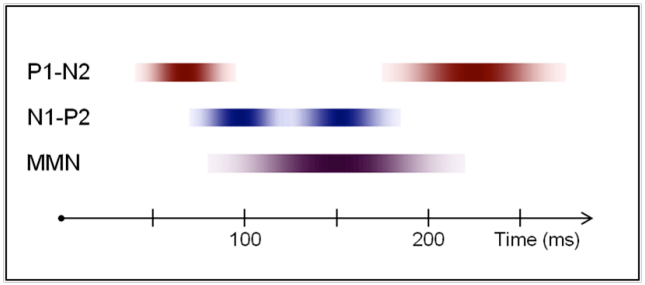


*Figure 1.* The schematic picture of the ERP components overlapping at the MMN time window in 9 to 11-year-old children. Latencies are based on Ponton et al., 2000.

There is a large body of literature on MMN findings in children (for a review, see Bishop, Anderson, Reid, & Fox, 2011), but an absence of developmental studies employing valid control conditions for MMN. Although several such studies in adults already exist in the auditory (Schröger & Wolff, 1996; Jacobsen & Schröger, 2001, 2003; Jacobsen, Schröger, Horenkamp, & Winkler, 2003; Opitz, Schröger, & Von Cramon, 2005; Maess, Jacobsen, Schröger, & Friederici, 2007; Horváth et al., 2008; Cheng et al., 2010; Hsu et al., 2010; Grimm, Escera, Slabu, & Costa-Faidella, 2011; Ruhnau, Herrmann, & Schröger, 2012) and visual (Pazo-Alvarez, Amenedo, & Cadaveira, 2004; Astikainen, Lillstrang, & Ruusuvirta, 2008; Kimura, Katayama, Ohira, & Schröger, 2009) modalities, there are fewer studies examining speech stimulation (Jacobsen, Horváth, Schröger, Lattner, Widmann, & Winkler, 2004; Jacobsen, Schröger, & Alter, 2004; Laufer, Negishi, & Constable, 2009) and even less examining

children (Ruhnau, Herrmann, Maess, & Schröger, 2011). The only child study, to our knowledge (Ruhnau et al., 2011), using a control condition studied maturation of N1 rather than MMN. They concluded N1 being mature already in 9-to-10-year-old children when comparing the responses to stimuli of repetitive and control conditions. Therefore, more developmental studies controlling MMN are needed due to the differences between adults and children in ERP morphology and timing. The present paper examines separate time courses and topographies in school-aged children in responses to speech and non-verbal stimulation in both classic oddball and equal probability (EQ) control condition. The EQ control condition was first introduced by Schröger & Wolff (1996) to control for the state of refractoriness of location-specific neurons. They found a fronto-central negative brain activity to be an automatic higher-order change detection process, or genuine MMN, that was separate from refractoriness effects.

The major objective of this study is to separate the MMN component temporally and spatially from the obligatory components occurring at the same latency in children. To clarify the role of the stimulus context, a prerequisite for the memory trace formation for the standard stimuli, the brain responses in the oddball condition were compared to those recorded in an EQ condition (for details, see below). MMN is usually studied using tones or speech sounds. To see the overlap for both types of stimuli vowel change and corresponding non-speech stimuli were used. To ensure the presence of MMN reflecting change detection based on the context of repeated standard stimulation, two contrasts were investigated: the classical deviant minus standard and deviant minus control response. We also assumed that the deviant response reflecting MMN should show a fronto-central scalp topography accompanied by a polarity reversal at the temporal areas below the Sylvian fissure.

# Method

## Participants

The 50 participants in this study (25 males, 25 females) were normally developing Finnish speaking children with mean age of 10.27 years (SD .43, range 9.55 – 11.05). They were recruited to a collaborative cross-linguistic event-related potential (ERP) study carried out in four European universities as a part of the European Sixth Framework Programme project *NeuroDys, Dyslexia genes and neurobiological pathways* (see www.neurodys.com). The participants were recruited according to institutional informed consent procedures approved by the Ethical Committee of the Central Hospital of Central Finland. All participants had an IQ of at least 85 as measured with non-verbal (Block design) and verbal (Similarities) subscales of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III: Wechsler, 1991). They had normal hearing levels measured with an audiogram with the average hearing threshold at the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz being at or below 20 dB. Forty-five of the participants were right-handed, 3 left-handed, and 2 ambidexterous (tested with the Edinburgh inventory; Oldfield, 1971).

## Stimuli

The stimulus set examined in the present paper consisted of 2 synthetic vowels (Finnish-Hungarian /y/ containing 10 formants and /i/ containing 9 formants), and 2 corresponding complex non-speech stimuli consisting of sine tones of the same frequencies as the vowel stimuli except the four highest. The formant frequencies and intensities are presented in Fig. 2. Altogether the study involved three different stimulus sets in separate blocks with the prototypical /y/ of each language group (the Finnish-Hungarian /y/, French /y/, and German /y/) presented as a deviant and the same common 'euro'-/i/ as a standard stimuli in each block (or their corresponding non-speech counterparts), but the current paper examined the results only for the ERPs recorded in the Finnish-Hungarian speech and non-speech blocks. For the details of creating and selecting the stimuli, see Bruder et al., 2011a; 2011b.

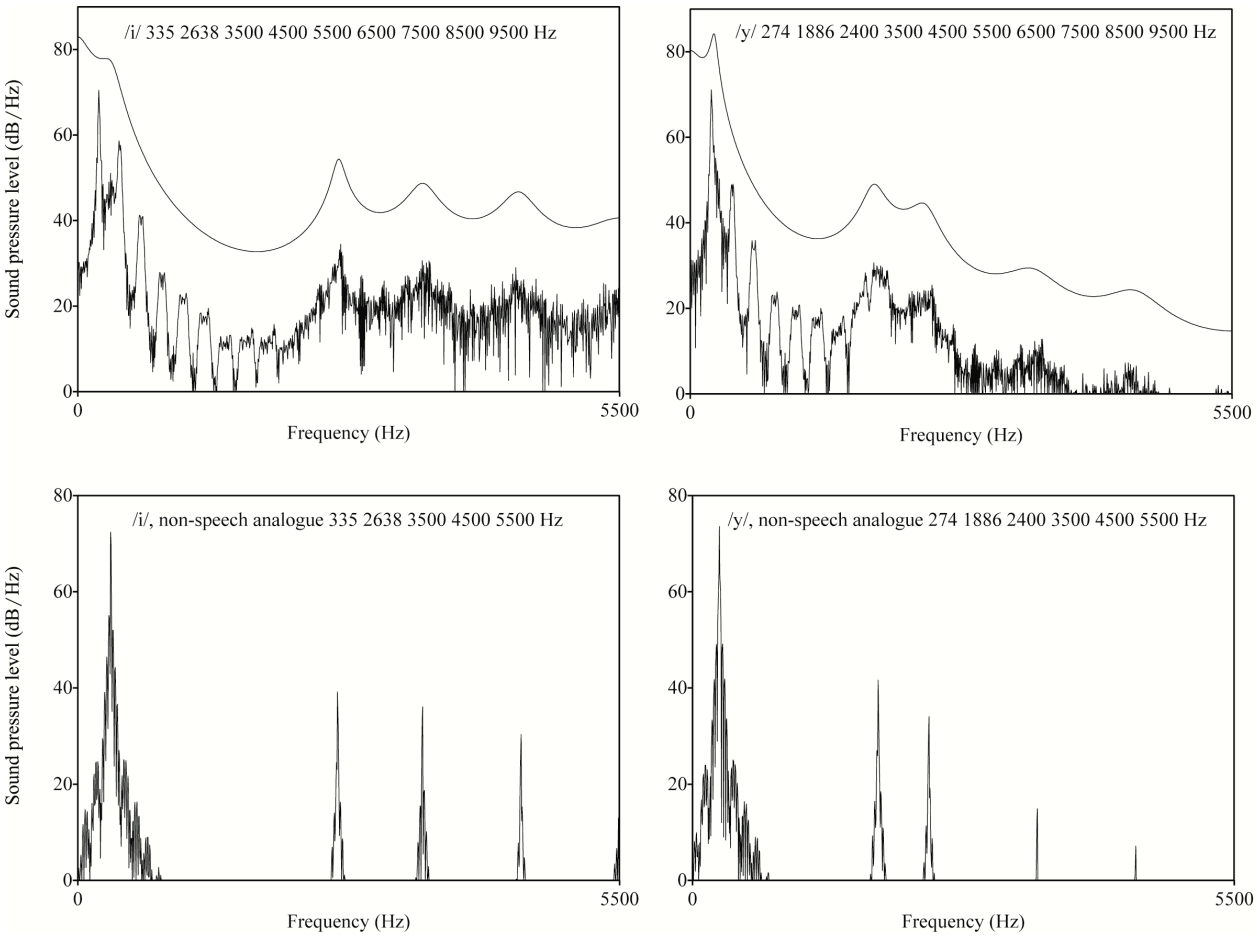


*Figure 2.* The narrow band spectra of the stimuli showing the harmonic structure of the stimuli. The overlaid LPC spectrum (the smoother line, only displayed in vowels) estimates the vocal track transfer function and shows the positions of the formants.

## Procedure

Stimuli were presented in pseudorandomized stimulus sequences in passive oddball and EQ conditions. Speech and non-speech stimuli were presented in separate oddball conditions. The order of the blocks was counterbalanced between participants, but the blocks with the non-speech stimuli were always presented first to prevent participants from perceiving the non-speech stimuli as speech. The control condition was presented after the oddball conditions. There were 129 deviant stimuli (vowel /y/ or its non-speech equivalent) with 18 % probability among 588 standard stimuli (vowel /i/ or its non-speech equivalent; 82%). In the control EQ condition the native speech and corresponding non-speech stimuli (/i/ and Finnish-Hungarian /y/ (from now on referred to as /y/) and their non-speech equivalents) were presented together each with an equal probability (25%), each stimulus occurring 129 times. In all conditions the stimulus onset asynchrony (SOA) varied pseudo-randomly between 600 – 700 ms

(average 650 ms). The intensities of the stimuli were separately measured with Brüel & Kjær sound level meter (type 2235), adjusted to equal intensity of approximately 70 dBA and presented binaurally via PX200 Sennheiser headphones.

### EEG Recording

The EEG was recorded with Ag-AgCl electrodes using 128-channel (Electric Geodesics Inc.) HydroCel Geodesic Sensor Nets and NetStation 4.2.1 software (www.egi.com/netstation.html). The EEG was referred to the Cz electrode and recorded with the sampling rate of 500 Hz and the bandpass filter of 0.1 – 200 Hz. Electro-oculogram (EOG) was recorded with electrodes located above, below and lateral to both eyes. All electrode impedances were pursued to be kept below 50 kΩ (quality of the data was monitored and electrode contact corrected as necessary during the recording). During the experiment, participants watched a self-selected silent video and they were instructed not to pay any attention to the stimulus sounds.

### Pre-processing of EEG Data

The data were pre-processed using BESA 5.1.8 software (www.besa.de). The EEG data were digitally filtered offline with a low cut off filter of 0.3 Hz and a high cut off filter of 30 Hz (both with 12 dB/octave roll off and a filter type zero phase). To additionally remove electric noise, the notch filter was set to 50.0 Hz with the width of 2.0 Hz. Eye blinks in the data were corrected before averaging with an individual eye blink correction algorithm implemented in BESA using PCA (Ille, Berg, & Scherg, 2002). ERPs to each stimulus type were obtained separately by averaging EEG epochs of -50 – 600 ms after the stimulus presentation and baselined to -50 – 0 ms. Channels with multiple artefacts throughout the data were set to bad and omitted from the averaging. EEG epochs with the voltage deflections exceeding ±200 μV were also excluded from the averaging as artefacts. The mean number of accepted epochs for averaging per stimulus type was 121 (range 100 – 129). For the standard stimuli, only the responses to the pre-deviant standard stimuli were included in the average for having an equal signal-to-noise ratio with other stimuli. After the averaging, the channels previously set as bad channels were interpolated using a spherical spline interpolation method (Perrin, Pernier, Bertrand, & Echallier, 1989). ERPs were transformed into reference free current source density (CSD) waveforms by computing a second spatial derivative by spherical spline interpolation (order of splines: 4; maximal degree of Legendre polynomials: 50; approximation parameter Lambda:

1.0e−005) using information from all electrodes resulting in the interpolation to the standard 81 channels of the 10-10 system (Perrin et al., 1989). CSD transformation acts as a spatial filter and is proven to be useful in sharpening and summarizing the broad ERP voltage topographies improving both the spatial and temporal resolution (Law, Rohrbaugh, Adams, & Eckardt, 1993; Nunez, 1981; Nunez & Srinivasan, 2006) and it also acts as a valuable pre-processing step for temporal principal component analysis (tPCA) (Kayser & Tenke, 2006).

**Statistical Analyses**

Temporal PCA using covariance matrix and Promax rotation was performed for the CSD transformed waveforms as a data reduction method to capture the richness of high-density recordings (Spencer, Dien, & Donchin, 1999; Kayser & Tenke, 2006). The purpose of tPCA was to isolate MMN from other overlapping auditory ERP components as it has been shown to work well in separating overlapping ERP components (Spencer et al., 1999; Kayser & Tenke, 2006; Pourtois, Delplanque, Michel, & Vuilleumier, 2008; Hämäläinen, Leppänen, Guttorm, & Lyytinen, 2007; 2008). Temporal PCA exploits the correlational structure of the waveforms to identify common patterns of covariance across participants, conditions and scalp locations (Coles, Gratton, & Fabiani, 1990; Dien, 2010). PCA takes into account all information in the data and distributes it into a set of maximally decorrelating factors (i.e. principal components), which in tPCA are derived by grouping together amplitude values at different time points that tend to vary in a correlated manner, as would be expected from the time points reflecting a common cognitive process. To maximize the chance that each factor reflects a unique underlying process, which may, however, correlate with each other, the tPCA solution was Promax rotated after the initial factor extraction (Hendrickson & White, 1964; Dien, Beal, & Berg, 2005; Dien & Frishkoff, 2005; Dien, 2010).

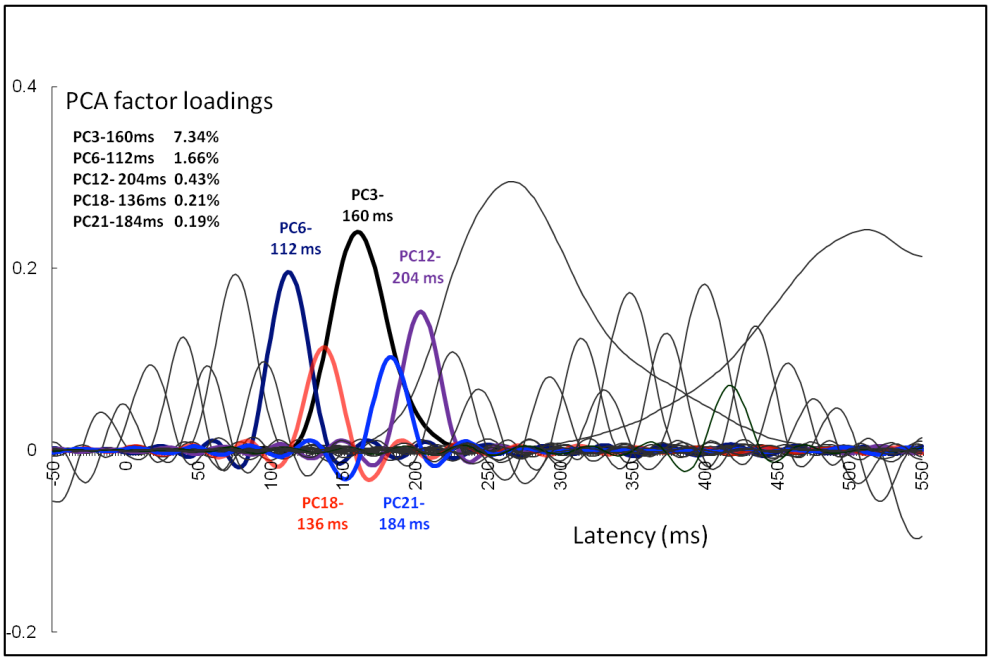


*Figure 3.* Factor loadings of the first 28 components (explaining altogether 99 % of the variance) of the tPCA. Five components selected for the further analysis in the MMN time window bolded and named by their order numbers and peak latencies. The percentages of variance explained by the PCs after Promax rotation are shown in the upper left corner.

Temporal PCA was applied for the CSD transformed averaged waveforms for time points ranging from 50 ms pre-stimulus to 550 ms post-stimulus across all participants, stimuli, conditions, and channels (Fig. 3). All temporal principal components (PCs) accounting for a total of 99% of the variance were included in the rotation (Kayser & Tenke, 2003). The PCs occurring at the latencies typically reported in the literature for MMN and showing comparable topographic distribution between the grand averaged CSD maps and PCA factor score maps were selected for further statistical analyses to test if they contained a change detection processing part besides the obligatory processing portion. The PCs to be used in the statistical analysis (see Fig. 3), peaking between 112 to 204 ms, were determined based on literature of the occurrence of MMN (100 – 200 ms), visual inspection of the occurrence of the responses to the standard and the deviant stimuli as well as peaking of the difference waves in the original averaged and CSD transformed waveforms (94 – 230 ms), and using *t*-tests against zero for the PCs (between 100 and 204 ms). Electrodes with largest amplitudes were chosen for analyses and the factor scores of the selected temporal PCs at these electrodes were separately tested against zero to ensure that the components of interest showed a systematic activation pattern. Multivariate analyses of variance (MANOVAs) were performed separately for non-speech and speech stimulus types for five selected principal component factor scores and

electrode clusters at fronto-central and inferior and posterior temporal scalp sites. Four electrode clusters were computed by averaging the responses at the left fronto-central (F5, FC5, C5), right fronto-central (F6, FC6, C6), left temporal (P7, TP9), and right temporal (P8, TP10) electrodes. The MANOVA model for repeated measures including Stimulus (standard, deviant) × Hemisphere (left, right) as within subject factors were used to test the deviant-standard contrast and the corresponding MANOVA model including Stimulus (deviant, control) × Hemisphere (left, right) to test the deviant-control contrast. The post hoc analyses were conducted using paired *t*-tests with Bonferroni corrected *p*-values.

## Results

Visual inspection of the waveforms revealed that the same stimulus presented as a deviant in the oddball condition (with a probability of 18 %) or when presented in the EQ condition with the same ISI and approximately the same overall probability (25 %) resulted in similar shaped waveforms differing in amplitude values. In the non-speech paradigm, the responses elicited in the two conditions began to diverge around 90 – 100 ms bilaterally having more negative amplitude at the fronto-central and more positive response at the temporal recording sites in the oddball condition than in the EQ condition (see Fig. 4d). The responses to speech stimuli had more negative amplitude in the oddball condition after 130 ms at the fronto-central and more positive amplitude after 100 ms at the temporal electrodes compared to the responses elicited in the EQ condition, the deviance of the responses beginning slightly earlier at right hemisphere (see Fig. 5d).

Principal component analysis (PCA) resulted in 28 temporal principal components (PCs), of which five peaked at the typically observed MMN time window between 100 – 200 ms, and were therefore selected for further statistical analyses (Fig. 3). The percentages of the total variance, which the selected five PCs explained after Promax rotation, are seen in the Fig. 3. The PCs have been named by their order number and peak latency. Four electrode clusters were computed by averaging the factor scores of left fronto-central (F5, FC5, C5), right fronto-central (F6, FC6, C6), left temporal (P7, TP9), and right temporal (P8, TP10) electrodes. Multivariate analyses of variance (MANOVA) were applied separately for each of the five PCs using fronto-central or temporal electrode clusters to test the two contrasts for MMN: the deviant-standard and deviant-control.

### Non-speech Stimuli

For the non-speech stimuli both the deviant-standard and the deviant-control contrasts were tested for PCs peaking at 112 ms, 136 ms, 160 ms, 184 ms, and 204 ms fronto-centrally as well as below the Sylvian fissure. The criteria for MMN were met for three earliest PCs. Albeit there were significant effects also for later PCs, contrary to the MMN waveform pattern, the responses to the standard stimuli were larger than to the deviant. All significant effects are reported below. Post hoc *t*-test *p*-values are Bonferroni corrected. MANOVA statistics for the non-speech stimuli are presented in Table 1.

Table 1

*MANOVA Test Statistics for Complex Non-speech Stimuli: the Deviant-standard and Deviant-control Contrasts*

| | PC6-112ms | | PC18-136ms | | PC3-160ms | | PC21-184ms | | PC12-204ms | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Fronto-central site** | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ |
| Deviant-standard: | | | | | | | | | | |
| Stimulus | 35.75***[c] | .42 | 29.38***[c] | .38 | 12.61**[c] | .21 | 0.05 | .00 | 0.80 | .02 |
| Hemisphere | 7.36**[a] | .13 | 3.48 | .07 | 1.86 | .04 | 2.49 | .05 | 5.12*[a] | .10 |
| Stimulus × Hemisphere | 10.05** | .17 | 2.24 | .04 | 0.77 | .02 | 1.49 | .03 | 6.40* | .12 |
| Deviant-control: | | | | | | | | | | |
| Stimulus | 6.53*[e] | .12 | 12.19**[e] | .20 | 8.16**[e] | .14 | 0.69 | .01 | 2.86 | .06 |
| Hemisphere | 12.87**[a] | .21 | 3.58 | .07 | 3.23 | .06 | 2.632 | .05 | 2.57 | .05 |
| Stimulus × Hemisphere | 4.81* | .09 | 3.00 | .06 | 0.09 | .00 | 2.19 | .04 | 3.79 | .07 |
| **Temporal site** | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ |
| Deviant-standard: | | | | | | | | | | |
| Stimulus | 64.19***[c] | .57 | 58.007***[c] | .54 | 20.46***[c] | .30 | 7.29*[d] | .13 | 5.11*[d] | .09 |
| Hemisphere | 18.362***[a] | .27 | 10.80**[a] | .18 | 0.09 | .00 | 3.29 | .06 | 0.98 | .02 |
| Stimulus × Hemisphere | 0.02 | .00 | .037 | .00 | 0.10 | .00 | 3.54 | .07 | 2.42 | .05 |
| Deviant-control: | | | | | | | | | | |
| Stimulus | 15.00***[e] | .23 | 15.751***[e] | .24 | 5.70*[e] | .10 | 0.00 | .00 | 0.62 | .01 |
| Hemisphere | 15.33***[a] | .24 | 8.531**[a] | .15 | 0.03 | .00 | 7.05*[b] | .13 | 6.23*[b] | .11 |
| Stimulus × Hemisphere | 0.01 | .00 | 0.211 | .00 | 0.07 | .00 | 0.48 | .01 | 0.266 | .01 |

*Note.* $\eta_p^2$, partial eta-squared; *$p$ < .05; **$p$ < .01; ***$p$ < .001; [a] left < right, [b] left > right, [c] deviant > standard, [d] deviant < standard, [e] deviant > control, [f] deviant < control.

*PC6-112ms:* The MANOVA yielded main effects for stimulus (deviant, standard) ($p < .001$; deviant > standard) and hemisphere ($p = .009$; left < right) as well as a Stimulus (deviant, standard) × Hemisphere interaction ($p = .003$) at fronto-central sites originating from a larger response to the deviant at left ($t(49) = 3.70$, $p = .002$, $d = .52$) and right ($t(49) = 6.72$, $p < .001$, $d = .95$) hemisphere as compared to the standard at left hemisphere. Also for the deviant-control contrast a stimulus (deviant, control) ($p = .014$; deviant > control) and hemisphere ($p = .001$; left < right) main effects and a Stimulus (deviant, control) × Hemisphere interaction ($p = .033$) were found. The interaction was explained by the larger response to the deviant at right hemisphere as compared to the left hemisphere ($t(49) = 3.86$, $p < .001$, $d = .55$). At the temporal scalp areas stimulus main effects (deviant > standard; deviant > control) and hemisphere main effects (left < right) were shown for both contrasts ($ps < .001$).

*PC18-136ms:* Stimulus (deviant, standard; deviant, control) main effects were shown at the fronto-central ($p < .001$; deviant > standard and $p = .001$; deviant > control) and temporal ($ps < .001$) scalp areas for both contrasts. At the temporal scalp areas also a main effect for hemisphere (right hemispheric dominance) was shown for the deviant-standard and deviant-control contrasts ($p = .002$ and $p = .005$, respectively).

*PC3-160ms:* Stimulus (deviant, standard; deviant, control) main effects were significant at fronto-central ($p = .001$; deviant > standard and $p = .006$; deviant > control) and temporal ($p < .001$; deviant > standard and $p = .021$; deviant > control) scalp areas.

*PC21-184ms:* At the temporal sites a stimulus (deviant, standard) main effect ($p = .010$; deviant < standard) as well as for the deviant-control contrast a hemisphere main effect were significant ($p = .011$; left > right). No significant effects were found at fronto-central sites.

*PC12-204ms:* Similarly to the previous component, at the temporal sites a stimulus (deviant, standard) main effect ($p = 0.28$; deviant < standard) and a hemisphere main effect ($p = .016$; left > right) were found. For the deviant-standard contrast at the fronto-central sites a hemisphere main effect ($p = .028$; left < right) and a Stimulus (deviant, standard) × Hemisphere interaction ($p = .015$) were shown. The interaction was explained by the larger response to the standard at right hemisphere as compared to the left hemisphere ($t(49) = 3.55$, $p = .003$, $d = .50$).

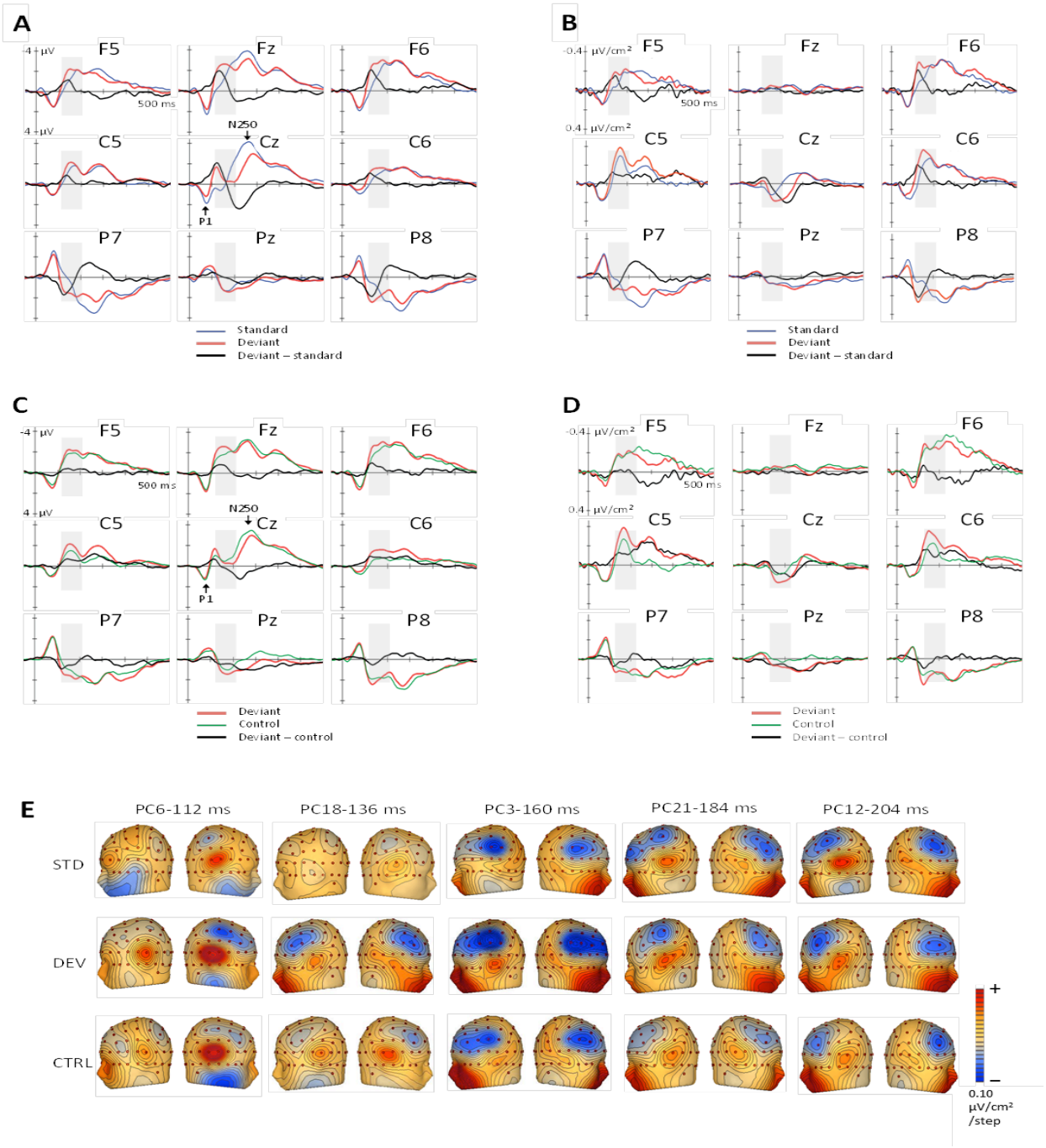


*Figure 4.* Grand average original ERP (A, C) and CSD waveforms (B, D) of 50 school-aged children for non-speech stimuli, and the topographic maps of the factor scores (E). Vertical tick marks represent 2 µV for ERP and 0.2 µV/cm$^2$ for CSD waveforms (negativity up); Horizontal tick marks represent 100 ms.
(A, B) The responses for the deviant (red line) and the standard (blue line) stimulus in the oddball condition accompanied with the deviant minus standard difference waveform (black line).
(C, D) The responses for the deviant stimulus in the oddball condition (red line) and for the same stimulus in the EQ condition, i.e. control (green line) and the deviant minus control difference waveform (black line). The grey area represents the time window of 112-204 ms.

**Speech Stimuli**

For the speech stimuli both the deviant-standard and the deviant-control contrasts were significant at the fronto-central channels for the four last PCs peaking at 136 ms, 160 ms, 184 ms, and 204 ms, but only at 160 ms were the both contrasts significant below the Sylvian fissure. All significant effects are reported below. MANOVA statistics for the non-speech stimuli are presented in Table 2.

*PC6-112ms:* A Stimulus (deviant, standard) × Hemisphere interaction ($p$ = .017) was found at the fronto-central areas. None of the post hoc t-test showed significant results, but the interaction seems to be originating from a larger response to deviant stimulus at right hemisphere as compared to the standard stimulus at left hemisphere. Also a Stimulus (deviant, control) × Hemisphere interaction ($p$ = .029) was found that was caused by a larger response to the control stimulus as compared to the deviant at left hemisphere ($t$(49) = 2.74, $p$ = .026, $d$ = .38). At the temporal scalp areas stimulus (deviant, standard) ($p$ = .021; deviant > standard) and hemisphere ($p$ < .001; left < right) main effects were shown, as well as a Stimulus (deviant, standard) × Hemisphere interaction ($p$ = .022). The interaction originated from a larger response to deviant stimulus at right hemisphere as compared to the standard at left hemisphere ($t$(49) = -5.25, $p$ < .001, $d$ = .74). For the deviant-control contrast a hemisphere main effect ($p$ < .001; left < right) originating from right hemispheric dominance was found.

*PC18-136ms:* A stimulus (deviant, standard) main effect ($p$ = .018; deviant > standard) and a stimulus (deviant, control) main effect ($p$ = .002; deviant < control) were found at the fronto-central sites. For the deviant-control contrast there was also a Stimulus (deviant, control) × Hemisphere interaction ($p$ = .030) explained by a larger response to the control stimulus as compared to the deviant at left hemisphere ($t$(49) = 3.915, $p$ = .002, $d$ = .55). At the temporal scalp areas there was a stimulus (deviant, standard) main effect ($p$ < .001; deviant > standard) and a hemisphere main effect for the both deviant-standard and deviant-control contrasts showing right hemispheric dominance ($p$ = .001 and $p$ = .004, respectively).

*PC3-160ms:* For both contrasts stimulus (deviant, standard; deviant, control) main effects were found with the response to the deviant stimulus being larger than to the standard or the control stimulus at the fronto-central ($p$ < .001 and $p$ = .005, respectively) and temporal ($p$ = .001 and $p$ < .001, respectively) scalp areas.

*PC21-184ms:* For the both contrasts stimulus (deviant, standard; deviant, control) main effects indicated larger responses to the deviant stimulus at the fronto-central areas ($p$ = .012 and $p$ < .001, respectively). At the

temporal scalp areas only a hemisphere main effect ($p$ = .044) for the deviant-standard contrast showing left hemispheric dominance was found.

*PC12-204ms:* Stimulus main effects ($p$ < .001; deviant > standard, and $p$ = .001; deviant > control) and hemisphere main effects ($p$ = .011 and $p$ = .003, respectively; left < right) were found for both contrasts at the fronto-central sites. At the temporal sites there was a Stimulus (deviant, standard) × Hemisphere interaction ($p$ = .009) which was caused by a significantly larger response to the standard stimulus at right hemisphere than at left hemisphere ($t(49) = 2.82$, $p$ = .021, $d$ = .40).

Table 2

*MANOVA Test Statistics for Synthetic Speech Stimuli: the Deviant-standard and Deviant-control Contrasts*

| | PC6-112ms | | PC18-136ms | | PC3-160ms | | PC21-184ms | | PC12-204ms | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Fronto-central site** | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ |
| Deviant-standard: | | | | | | | | | | |
| Stimulus | 3.00 | .06 | 5.94* [c] | .11 | 39.92*** [c] | .45 | 6.87* [c] | .12 | 14.50*** [c] | .23 |
| Hemisphere | 0.21 | .00 | 0.02 | .00 | 0.42 | .01 | 1.33 | .03 | 7.00* [a] | .13 |
| Stimulus × Hemisphere | 6.10* | .11 | 0.41 | .01 | 1.58 | .03 | 0.53 | .01 | 0.03 | .00 |
| Deviant-control: | | | | | | | | | | |
| Stimulus | 2.20 | .04 | 11.17** [f] | .19 | 8.57** [e] | .15 | 14.95*** [e] | .23 | 12.67** [e] | .21 |
| Hemisphere | 0.15 | .00 | 0.82 | .02 | 0.45 | .01 | 1.29 | .03 | 9.77** [a] | .17 |
| Stimulus × Hemisphere | 5.04* | .09 | 4.99* | .09 | 1.14 | .02 | 0.27 | .01 | 0.00 | .00 |
| **Temporal site** | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ | *F*(1, 49) | $\eta_p^2$ |
| Deviant-standard: | | | | | | | | | | |
| Stimulus | 5.64* [c] | .10 | 26.84*** [c] | .35 | 13.46** [c] | .22 | 1.78 | .04 | 0.01 | .00 |
| Hemisphere | 24.82*** [a] | .34 | 11.94** [a] | .20 | 0.02 | .00 | 4.28* [b] | .08 | 1.43 | .03 |
| Stimulus × Hemisphere | 5.57* | .10 | 1.25 | .03 | 1.18 | .02 | 1.26 | .03 | 7.36** | .13 |
| Deviant-control: | | | | | | | | | | |
| Stimulus | 1.06 | .02 | 1.27 | .03 | 15.36*** [e] | .24 | 3.69 | .07 | 1.75 | .03 |
| Hemisphere | 21.81*** [a] | .31 | 8.95** [a] | .15 | 0.18 | .00 | 0.42 | .01 | 0.01 | .00 |
| Stimulus × Hemisphere | 2.41 | .05 | 1.151 | .02 | 0.54 | .01 | 0.65 | .01 | 0.713 | .01 |

*Note.* $\eta_p^2$, partial eta-squared; *$p$ < .05; **$p$ < .01; ***$p$ < .001; [a] left < right, [b] left > right, [c] deviant > standard, [d] deviant < standard, [e] deviant > control, [f] deviant < control.

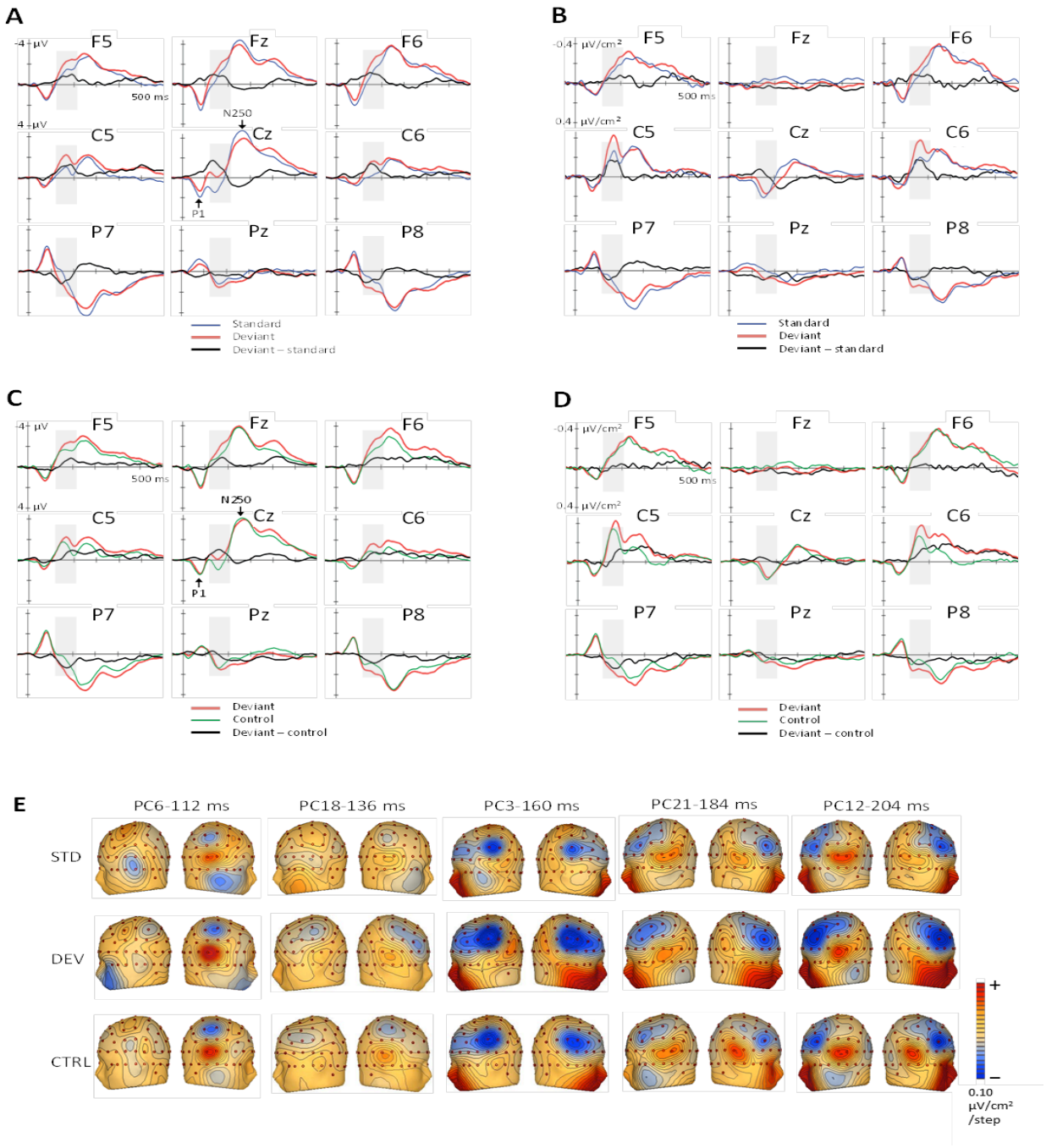


*Figure 5.* Grand average original ERP (A, C) and CSD waveforms (B, D) of 50 school-aged children for speech stimuli, and the topographic maps of the factor scores (E). Vertical tick marks represent 2 µV for ERP and 0.2 µV/cm$^2$ for CSD waveforms (negativity up); Horizontal tick marks represent 100 ms.
(A, B) The responses for the deviant (red line) and the standard (blue line) stimulus in the oddball condition accompanied with the deviant minus standard difference waveform (black line).
(C, D) The responses for the deviant stimulus in the oddball condition (red line) and for the same stimulus in the EQ condition, i.e. control (green line) and the deviant minus control difference waveform (black line). The grey area represents the time window of 112-204 ms.

## Discussion

Since Schröger & Wolff (1996) introduced the equal probability (EQ) condition for controlling effects of neural refractoriness and afferent activation on MMN, many studies exploiting auditory stimuli in adults (Schröger & Wolff, 1996; Jacobsen & Schröger, 2001; Jacobsen & Schröger, 2003; Jacobsen et al., 2003; Opitz et al., 2005; Maess et al., 2007; Horváth et al., 2008; Cheng et al., 2010; Hsu et al., 2010; Grimm et al., 2011; Ruhnau et al., 2012) have utilized the condition to confirm their results. However, there is a lack of studies controlling refractoriness and afferent effects on the responses at a typical MMN latency in children. These studies are important, especially in view of the dissimilarities between the ERPs of children and adults. In this study we examined the ERP responses of 9-11-year-old children and found, similarly to Schröger & Wolff (1996) in adults, that the difference between the deviant and standard responses alone is not a sufficient condition for defining MMN generated by speech stimuli. By employing both oddball and EQ conditions we found that MMN to synthesized vowel /y/ vs. /i/ stimuli emerged only at 160 ms when the differences in two contrasts (deviant-standard and deviant-control) were used as the criteria. Instead, when only the deviant-standard criterion was used, MMN to speech sounds seemed to emerge already at 112 ms. No latency difference was observed for MMN to non-speech with either criterion.

The aim of the present study was to detect mismatch negativity among the obligatory ERP components in school-aged children in response to speech and corresponding non-speech stimuli. CSD transformation (Perrin, Pernier, Bertrand, & Echallier, 1989) and temporal PCA (Kayser & Tenke, 2006) were applied to gain better separation of the MMN component from other simultaneously emerging components. CSD transformation clarified the picture of the underlying cortical activities, and PCA, which has been previously successfully used in other child ERP studies (e.g. Hämäläinen et al., 2007, 2008), acted as an efficient method for finding the time points of interest. CSD-PCA approach has been suggested to serve as a link between scalp potentials and anatomically-relevant current generators (Kayser & Tenke, 2006). Five principal components (PCs) were found to reflect discriminatory processing as well as obligatory responses in the typical MMN time window of 100 – 200 ms.

Although the PCA procedure itself did not highlight any specific MMN components it efficiently separated several latency ranges with systematic response variation within the MMN time window, presumably

reflecting different phases of auditory processing. The employment of the EQ condition for PCA factor scores helped to determine which of those phases reflected processing of change detection instead of obligatory or exogenous response. As is evident from the data (Fig. 4 and 5), the separation of time ranges into these different responses could not have been possible by traditional peak analyses due to the lack of clear peaks and overlapping responses.

In response to the non-speech stimuli, the change detection processing was present in the principal components with maximum loadings at 112, 136, and 160 ms at both the fronto-central areas and below the Sylvian fissure at the inferior-posterior temporal scalp areas. The speech stimuli generated MMN which was detected fronto-centrally in the PCs loading maximally at 136, 160, 184, and 204 ms, but below the Sylvian fissure only in the component at 160 ms. These latency differences between MMN to the non-speech and speech stimuli cannot be attributed to a difference in the rise times of the non-speech and speech stimuli since the difference between the time from stimulus onset to the point when the sound gained its maximum intensity varied only 2 – 3 ms between the speech stimulus and its non-speech equivalent. More likely, the latency difference is due to the complexity of the stimuli; the speech stimuli contained more frequency bands than the non-speech stimuli and, in addition, a glottal pulse embedded in them (Bruder et al., 2011a; 2011b). Furthermore, the top-down processing of speech stimuli, due to the long term representations of the native /y/ and /i/ vowels, is likely to play a role in the MMN differences between speech and non-speech stimuli. Using Finnish vowels Jaramillo et al. (2001) observed that in adults speech stimuli were more efficiently processed than harmonical tones causing an enhanced MMN (Jaramillo, Ilvonen, Kujala, Alku, Tervaniemi, & Alho, 2001), which they suggested to arise due to native speech sounds activating long-term memory traces more easily and readily than unfamiliar sounds. However, the same kind of MMN enhancement for speech stimuli was not detected in the present study, which can be caused by differences in stimuli and by developmental issues.

Our present findings regarding MMN generated by speech stimuli are in line with earlier studies reporting temporal and frontal sources of MMN in children (e.g. Gomot et al., 2000). The response observed below the Sylvian fissure has been suggested to reflect mainly supratemporal sources of the MMN, while the fronto-central activity is thought to be summation of the supratemporal sources and the frontal source of the MMN (Näätänen et al., 1978; Baldeweg, Williams, & Gruzelier, 1999; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Näätänen et al., 2007). When looking at the difference between the responses to the deviant /y/ and the standard /i/ (deviant-

standard), a discriminatory response can be seen to emerge at the temporal sites already at 112 ms. The temporal activity was followed by partly overlapping fronto-central discriminatory components detected in the PCs peaking at 136, 160, 184, and 204 ms. This was also the case when investigating the deviant /y/ - control /y/ contrast at the fronto-central sites. However, for the deviant-control contrast, MMN at the temporal sites below the Sylvian fissure, presumably reflecting the supratemporal source, was not evident until in the PC at 160 ms. Therefore, when observing the areas below the Sylvian fissure, the difference between the responses to the standard /i/ and the deviant /y/ in the PCs for speech stimuli at 112 ms and 136 ms cannot be interpreted as a "genuine" MMN, but rather being clearly obligatory in nature, most likely representing the supratemporal source of N1 (see Figure 5e). This is concordant with the recent study of Ruhnau et al. (2011) observing an N1 wave already at the age of 9-10 years using a SOA of 500ms.

For non-speech stimuli the temporal and the frontal change detection activation seems to be simultaneous, both activations emerging after 100 ms and fading around 170 ms after the stimulus onset, regardless of which of the two criteria set for MMN in this paper is applied. Hence, it would be logical to argue that the later frontal change detection activation at around 180-200 ms observed only for the speech stimuli would be specific to speech, likely representing further discriminative processing of vowels or partly overlapping attention shift (Deouell, 2007). It is possible that the PC at 136 ms shows the onset of MMN processing in response to speech stimuli, reflecting more general change detection processing of acoustic characteristics, which rises to its maximal amplitude at about 160 ms. The following components at 184 ms and 204 ms thus seem to represent the fronto-central change detection processes of more complex features of speech (Jaramillo et al., 2001).

The latency of the MMN response was in line with earlier child studies. Approximately at the age of ten years, MMN has been reported to emerge at the latency of 137 – 198 ms (later for vowels than their non-speech counterparts), while the N1 is observed at the latency of 98 – 114 ms (Gomot et al., 2000; Ponton et al., 2000; Lepistö, Silokallio, Nieminen-von Wendt, Alku, Näätänen, & Kujala, 2006). This is in line with our results showing the emergence of MMN for non-speech at 112 ms and for speech at 160 ms. Previously, without a control condition, MMN in children has also been shown to have a longer latency for syllables than for tones, but not for vowels (Csépe, 1995).

The visual inspection of the topographic maps of the factor scores for the non-speech deviant stimulus and its control in the EQ condition reveals that the distributions are spatially similar, but the negativity is

significantly weaker in the EQ condition, already in the PC at 112 ms (Fig. 4e). Fronto-central negativity was observed in both conditions predominantly at the right hemisphere. For the speech stimuli, in contrast, a clear dipolar structure was seen as a central negativity and temporal positivity at the right hemisphere, which was similar in amplitude for the deviant and its EQ condition control stimulus (Fig. 5e). By 136 ms the negative response to the non-speech stimuli became bilateral and more frontal. The distributions of the responses to the deviant and the standard stimuli, as well as to the deviant stimulus and its EQ control differed clearly demonstrating separable MMN from the obligatory ERP. The responses to the /y/ stimulus at this latency in both oddball and EQ conditions were weaker than the responses to the non-speech stimuli, especially when compared to the non-speech deviant response. The distribution of the response to the deviant speech stimulus was more anterior and stronger at the right hemisphere compared to the left hemisphere. Although low in amplitude, the responses between the deviant and standard stimuli, as well as the deviant and its control stimuli, differed indicating an emerging MMN response for the speech stimuli. At 160 ms the distributions of the responses to the both non-speech and speech stimuli exposed an obvious bilateral MMN component. The positivity over temporal areas was stronger and the negativity appeared more frontally in response to the non-speech than to the speech stimuli. The more frontal distribution of the response to the non-speech deviant stimulus compared to the speech deviant stimulus could be due to the phase of the change detection process: for the non-speech stimuli MMN fades away after 160 ms, while for the speech stimuli, MMN has just emerged and still continues for 50 ms, probably indicating further processing of phonetic features of speech stimuli. In the non-speech condition, the PCs peaking at 184 ms and 204 ms show that the activation of the standard stimulus exceeds that of the deviant stimulus denoting the end of MMN. Similarly as at the end of the non-speech response, MMN in response to the speech stimuli shifts anteriorly (from central to frontal), being the most frontal at the last principal component at 204 ms.

Hemispheric effects at temporal recording sites for speech and non-speech stimuli were found in PCs peaking at 112 and 136 ms with right sided preponderance, and with left sided preponderance for speech in PC peaking at 184 ms and for non-speech in PCs peaking at 184 and 204 ms. At fronto-central sites the right hemispheric dominance was seen in the PC peaking at 204 ms for both stimulation types but only for non-speech stimuli in the earliest PC peaking at 112 ms. The predominance of the right hemisphere is in accordance with an earlier study of Korpilahti & Lang (1994) in school-aged healthy control children and with numerous studies with adults (Näätänen, Paavilainen, & Reinikainen, 1989; Paavilainen et al., 1991; Näätänen, 1992; Opitz, Mecklinger,

von Cramon, & Kruggel, 1999). Korpilahti & Lang (1994) found the MMN lateralization to the right hemisphere especially for the frequency stimuli as compared to the duration stimuli. However, usually the features of the speech stimuli, except for prosody, have been reported to be processed more at left hemisphere (cf. Price, 2012). In the present study, the hemispheric effects for speech stimuli could be related to the shortness and the synthetic nature of the stimuli or be also due to the fact that they could be discriminated only based on frequency cues (cf. Zatorre & Belin, 2001). However, it should be noted that in EEG the electrical fields spread while propagating through the head tissues and it is difficult to estimate accurately the brain areas responsible to the ERPs, even at a hemispheric level without source localization analyses (Otten & Rugg, 2005).

When interpreting the results of the present study, three issues related to the design should be considered. First, there was a slight difference between the probabilities with which the deviant and the control stimuli were presented (18% vs. 25%). However, considering this difference (7 %) in relation to the difference between the probabilities of the standard and deviant stimuli (64 %) it seems unlikely that the small 7% difference would be a confounding factor in the observed results. It should also be noted, that the higher probability in the EQ condition should lead to smaller ERP amplitudes in the EQ condition compared to the oddball condition for the deviant stimulus, which was not observed in the results. Second, presenting the non-speech condition always first before the speech condition could have caused some of the responses to the speech stimuli to attenuate. Therefore, the results for the MMN latency difference for the non-speech and speech sounds would need replication employing similar kind of control procedures as used here. Third, a common EQ condition was employed for the non-speech and speech stimuli, where all four stimuli were mixed randomly. One could argue that having two types of stimuli embedded in the same condition possibly has an effect on the perception of non-speech stimuli as speech, which in turn could produce categorization of the stimuli into two groups or alternatively cause the non-speech stimuli to appear more speech like in the EQ condition. This could be argued then to cause some difference in processing the same stimulus in the oddball and EQ conditions. However, when compared to the speech stimuli, the non-speech stimuli showed clearly differential and larger responses at the early latency in both oddball and EQ conditions. If the non-speech stimuli were perceived as speech in the EQ condition, the response strength should be similar between the stimulus types in the EQ condition, which was not the case. It is also assumed that MMN should not be generated in the EQ condition in any case, due to the lack of consecutively repeated standard stimulus. Therefore, it is safe to compare the responses of these conditions in relation to change detection processes.

As a following step, source localization of the ERP responses would be important to get a deeper understanding of the origin of brain activations of MMN-related change detection processes. Although the CSD transformation of ERP data already gives a better approximation of the original source activation by eliminating volume-conducted contributions (Kayser & Tenke, 2006) than the use of the field potentials, source localization can further improve the anatomical specificity and dissociate the time courses of the MMN sources.

To conclude, MMN can be teased apart from obligatory auditory brain responses by implementing an additional deviant-control contrast on top of the classical deviant-standard contrast. The implementation of the additional contrast had no effect on the latencies of MMN measured at fronto-central scalp sites. Instead, the differences in the MMN latency were observed at the recording sites below the Sylvian fissure. Without applying the additional deviant-control contrast, the difference in the responses to speech stimuli was observed to arise much earlier than when the deviant-control contrast was used. Based on the evidence from the present study, we conclude that the early temporal activation is obligatory in nature instead of representing a context based change detection process. MMN also emerges earlier for non-speech stimuli than for speech stimuli, when judged based on the the additional deviant-control contrast. Therefore, to separate memory trace based change detection processing from the obligatory afferent responses, the employment of the EQ condition is highly recommended.

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