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Event-related potentials to tones show differences between children with multiple risk factors for dyslexia and control children before the onset of formal reading instruction

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Abstract

Multiple risk factors can affect the development of specific reading problems or dyslexia. In addition to the most prevalent and studied risk factor, phonological processing, also auditory discrimination problems have been found in children and adults with reading difficulties. The present study examined 37 children between the ages of 5 and 6, 11 of which had multiple risk factors for developing reading problems. The children participated in a passive oddball EEG experiment with sinusoidal sounds with changes in sound frequency, duration, or intensity. The responses to the standard stimuli showed a negative voltage shift in children at risk for reading problems compared to control children at 107-215 ms in frontocentral areas corresponding to P1 offset and N250 onset. Source analyses showed that the difference originated from the left and right auditory cortices. Additionally, the children at risk for reading problems had a larger late discriminative negativity (LDN) response in amplitude for sound frequency change than the control children. The amplitudes at the P1-N250 time window showed correlations to letter knowledge and phonological identification whereas the amplitudes at the LDN time window correlated with verbal short-term memory and rapid naming. These results support the view that problems in basic auditory processing abilities precede the onset of reading instruction and can act as one of the risk factors for dyslexia.

Keywords: auditory processing, children, dyslexia, EEG, event-related potentials, mismatch negativity, N250, preschool

1. Introduction

Specific reading difficulty or dyslexia is one of the most common learning difficulties, affecting approximately 5-10% of the population (Vellutino et al., 2004). Besides problems in learning to read and write, individuals with dyslexia often have problems in phonological processing, verbal short-term memory, and rapid naming (Lyon et al., 2003; Vellutino et al., 2004). These three deficits have been found consistently across studies and phonological deficits are thought to be directly causal to development of reading problems (Bradley & Bryan, 1983; Wagner & Torgesen, 1987). However, other deficits have also been observed with varying consistency in, for example, more general language skills (Lyytinen et al., 2005), fine motor learning (Nicolson et al., 2001), binocular control (Stein et al., 2000) and auditory processing (Goswami, 2011; Tallal & Gaab, 2006).

The role of these other deficits remains unclear and the role of auditory deficits in the development of reading problems has been discussed extensively in the literature (e.g., Goswami, 2011; Hämäläinen et al., 2013b; Ramus, 2004; White et al., 2006). The connection between auditory and reading problems has been suggested to, be directly causal, further aggravating the already existing problems, one of many accumulating risk factors or co-occurring with no direct association (e.g., Bishop et al., 1999; Pennington, 2006; Ramus, 2004; Tallal, 1980). Most previous studies have examined the auditory processing abilities of either school-age children or adults with dyslexia (e.g., Corbera et al., 2006; Khan et al., 2011; Kujala et al., 2000; Lachmann et al., 2005; Hämäläinen et al., 2007; 2008) and thus the developmental relationship between auditory and reading or pre-reading skills is not clear. Only a handful of studies have examined the auditory processing abilities of children at risk for dyslexia before formal reading instruction has begun (e.g., Boets et al., 2006; Hämäläinen et al., 2013a; Leppänen et al., 2010; van Leuwen et al., 2006; Lovio et al., 2010; Maurer et al., 2003).

Examining the auditory processing abilities of children before reading instruction has started is important in disentangling the effect of reading acquisition, pre-reading skills and general brain maturation. During childhood, relatively fast maturation occurs in the brain and in the auditory cortices due to, for example, changes in synaptic connections, number of neurons, and myelination (Moore & Guan, 2001; Petanjek et al., 2011). One method to examine the time course of brain maturation is electroencephalography (EEG), which measures the fluctuations of electrical fields generated by the brain on the scalp surface. The majority of developmental EEG studies have been carried out with school-age children (e.g. Corbera et al., 2006; Hämäläinen et al., 2007; Lachmann et al., 2005). However, maturational changes in EEG occur rapidly already before school age (Albrecht et al., 2000; Choudhury et al., 2011; Ponton et al., 2000). The present study examined electrophysiological indices of auditory discrimination in children at preschool with and without risk factors for dyslexia.

Most sounds that generate activity in the cochlea nerve produce a series of responses in EEG, often called obligatory event-related potentials (ERPs), even without active attention to the sounds. In adults, this series of responses consists of P1, N1, P2, and N2 responses. They occur at approximately 50 ms, 100 ms, 150 ms, and 200 ms after the stimulus onset. The obligatory responses in children, on the other hand, show a drastically different morphology. With inter-stimulus intervals (ISIs) shorter than one second, the waveform of children younger than 10 years is characterized by P1 and N250 responses, emerging approximately 100 ms and 250 ms after stimulus onset (Sharma et al., 1997; Sussman et al., 2008). After 9 years of age, the N1-P2 complex starts to emerge and gradually grows in amplitude to adult values while the P1-N250 complex reduces in amplitude (Albrecht et al., 2000; Ceponiene et al., 2002; Ponton et al., 2000; 2002; Tonnquist, 1996, Wunderlich et al., 2006). The P1-N250 complex shows a fronto-central voltage distribution

and has sources close to the auditory cortex (Parviainen et al., 2011; Ponton et al., 2002). The exact functional significance of the obligatory responses is not clear, but they most likely reflect sound detection and complexity, formation of memory representations, categorization, and feature extraction processes (Karhu et al., 1997; Näätänen & Picton, 1987; Ceponiene et al., 2001).

Several studies have examined the obligatory responses in children with dyslexia. Some studies carried out at school age and using fast stimulation rates (below 1 s) have not found P1 or N250 amplitude or latency differences between individuals with dyslexia and controls (Lachmann et al., 2005; Sharma et al., 2006). However, group differences have been found in experiments where long ISIs (above 1 s) have been used and thus the N1-P2 responses are elicited. In an experiment where tones were presented with 2-2.5 second intervals in an active listening task, the P2 response was found to be enhanced in poor reading children compared to controls (Bernal et al., 2000). On the other hand, in a passive listening experiment, the P2 amplitude was reduced in children with dyslexia compared to controls when 1–5 second sound intervals were used (Hämäläinen et al., 2007). In the same experiment, the N1 response was found to be larger in amplitude in individuals with dyslexia compared to controls in a condition where sound pairs were presented and the second sound in the pair had a long rise time (Hämäläinen et al., 2007). However, in one study the same children as in Hämäläinen and colleagues (2007) were examined using source localization methods and smaller left hemispheric responses were found in children with dyslexia than children in the control group in an experiment where the ISI was short (610 ms) (Khan et al., 2011). The source activity was smaller at latencies centered around 128 ms and 180 ms (corresponding to the P1 and emerging P2), but only in a condition where tone pairs with short gaps (10 ms) were used (Khan et al., 2011). Thus the previous literature suggests differences between typically reading school-age children and children with dyslexia to

emerge in obligatory ERP responses at 100–200 ms, particularly, but not exclusively, when long ISIs are used.

Only two studies have been carried out at kindergarten age and examined the obligatory ERP responses in children at risk for dyslexia. The N250 response has been found to be larger in 6.5-year-old children who developed dyslexia at school age compared to controls and children who had a familial risk for dyslexia but developed reading skills at the normal level for both speech sounds and complex non-speech sounds (Hämäläinen et al., 2013a). Although it is not clear what processes the N250 response reflects, a larger N250 could be a marker of a less mature auditory cortex or a marker of more effortful memory trace formation (e.g., Karhu et al., 1997; Ponton et al., 2000). Additionally, the P1 response has been found to be smaller in 6.5-year-old children at risk for dyslexia compared to control children for speech sounds (Lovio et al., 2010). This finding was interpreted as a difficulty in establishing sound representations in the at-risk children (Lovio et al., 2010).

The above reviewed studies examined the obligatory ERPs. However, auditory discrimination ability can be studied more specifically using a response called the mismatch negativity (MMN; Näätänen et al., 1978; Näätänen et al., 2010). The MMN is generated when repetitive background stimulation is given and a sound is played that differs in some acoustic or more abstract feature from the background. This deviant sound elicits an ERP with negative voltage at frontocentral electrodes and positive voltage in areas below the Sylvian fissure, indicative of sources near the auditory cortex. There are also reports of a frontal source for the MMN response (e.g., Opitz et al., 2002; Rinne et al., 2000; Deouell, 2007). The MMN peaks between 150 and 250 ms after the onset of the deviant sound feature. Many types of deviant features elicit the MMN response, including changes in sound frequency, duration, and intensity, but also in sound onsets, sound omissions, and violations in abstract sound feature rules (Näätänen et al., 2010). Several studies have also shown that

the amplitude of the MMN response correlates with behavioral deviant sound detection accuracy (e.g., Novitski et al., 2004; Pakarinen et al., 2007) and that the MMN amplitude increases with improvement in behavioral discrimination ability after training (e.g., Atienza et al., 2002; Kraus et al. 1995; Näätänen et al., 1997).

In children between the ages of 6 and 13 years, MMN to frequency and duration changes has been reported to have similar or slightly longer peak latency (130 – 250 ms) compared to adults and to have a similar frontocentral negative topography (e.g., Ahmmed et al., 2008; Ceponiene et al., 1998; Corbera et al., 2006; Gomes et al., 1999; Huttunen et al., 2007; Hämäläinen et al., 2008; Korpilahti et al., 1994; Lachmann et al., 2005; Shafer et al., 2000; Sharma et al., 2006; Uwer & von Suchodoletz, 2000). At this age, MMN often seems to be accompanied by a second, longer latency frontocentral negative deflection starting after around 350 ms (Ceponiene et al., 2004; Hämäläinen et al., 2008; Schulte-Körne et al., 1998). In different studies, this late discriminative negativity (LDN) has also been termed late negativity or late mismatch negativity. However, its function is still unknown, with suggestions of involvement in further cognitive processing of the sound change, long-term memory storage, or activation of attention mechanisms (Ceponiene et al., 2004; Cheour et al., 2001; Shestakova et al., 2003; Zachau et al., 2005).

In preschool or kindergarten children there are fewer and more varied reports on the latency and topography of MMN compared to school-age children. Maurer and colleagues (2003) reported a positive fronto-central component at the latency of 150 ms in response to pitch and duration changes in both tones and speech stimuli and interpreted it as an MMN or mismatch response. They also observed a later negativity at circa 450 ms. However, Shafer and colleagues (2000) found a negative amplitude response to frequency change at a latency of 226-238 ms in children aged between 4 and 6 years. Holopainen and colleagues (1997) examined MMN to frequency change in children aged 5.2 years and found

frontocentral negative voltages peaking at 283 ms. Similarly, Korpilahti and colleagues (2001) reported an adult-like frontocentral negative component with a latency between 150 and 350 ms to a duration change in tones in children aged 5.7 years. Lovio and colleagues (2010) examined speech stimuli in children aged 6.4 years and also found a negative response with 150 ms latency elicited by changes in vowel frequency, duration, and intensity, as well as in vowel identity and consonant identity. Thus there are a few studies characterizing the MMN waveform at preschool age with most of them showing an adult-like frontocentral negativity with slightly longer peak latency than in adults.

Several studies have examined the MMN response in school-age children with dyslexia. Most of these studies have found a reduced MMN amplitude in response to small frequency changes and duration changes in children with dyslexia compared to control children (e.g., Corbera et al., 2006; Huttunen et al., 2007; Lachmann et al., 2005; for reviews, see Bishop, 2007; Hämäläinen et al., 2013b). However, one study found no group differences between children with and without dyslexia in the MMN amplitude to a small frequency change (Schulte-Körne et al., 1998).

Some studies have also examined the MMN response in kindergarten children at risk for dyslexia due to a family history of reading problems. The MMN amplitude has been found to be reduced in response to changes in tone frequency and consonant identity in speech sounds, although this was evident mostly at a late time window (Maurer et al., 2003). At an earlier time window the response was positive in polarity and children at risk for dyslexia showed slightly enhanced amplitude to the consonant change. In another study, reduced MMN was found for speech sounds with duration, intensity, vowel identity and consonant identity changes in children aged 6.4 years at risk for dyslexia compared to children in the control group (Lovio et al., 2010). In a recent study Plakas and colleagues (2012) examined 41-month-old children at risk for dyslexia and controls in an ERP

experiment. They showed that the at-risk children had atypically small MMNs to rise time and frequency changes. This smaller MMN in at-risk children was present regardless of the children's later reading outcome at the end of the Grade 2. They also showed that the ERP amplitude correlated with reading skills but not with phoneme deletion measured at the end of the second grade.

The previous literature thus shows evidence for basic auditory processing differences in school-age children with dyslexia and pre-reading children at risk for dyslexia albeit the evidence is not conclusive (e.g. Bishop, 2007; Hämäläinen et al., 2013). However, it is not known whether all basic auditory features show differences in the MMN response between the groups or whether they are restricted to frequency, rise time, and duration (e.g., Corbera et al., 2006; Maurer et al., 2003; Plakas et al., 2012). Additionally, it is not known how well the electrophysiological measures are correlated with behavioral measures of phonological processing and language skills. The present study, therefore, has three aims: One, to determine the change detection responses of kindergarten children to different sound feature deviations; Two, to examine differences in the obligatory, sound frequency, duration, and intensity processing between preschool children at risk for dyslexia and control children; Three, to examine the strength of the associations between the electrophysiological auditory processing indices and behavioral phonological and language abilities before reading instruction has begun.

Based on earlier studies we expected MMN to show similar topography, source locations and slightly longer latency to those found in adults (Lovio et al., 2010; Opitz et al., 2002; Plakas et al., 2012). We also expected the children at risk for dyslexia to differ in frequency and duration discrimination but not in intensity discrimination (Hämäläinen et al., 2013). If atypical auditory processing is connected to reading development, the ERP amplitudes should also show associations with phonological processing skills (e.g., Puolakanaho et al., 2004).

2. Methods

2.1. Participants

EEG data was recorded from 37 Finnish, monolingual, kindergarten children between the ages of 5 and 6 years with no history of neurological problems or serious head injuries. Out of these, 26 (13 boys, 13 girls) belonged to a control group with no history of learning disabilities and 11 had a family history of dyslexia (4 boys, 7 girls) based on a report from at least one parent having dyslexia. The control children were recruited from the same age range as the at-risk children. The children were recruited from the Central Finland area. All children had below 25 dB HL average hearing thresholds for 500–2000 Hz frequencies in both ears measured with an audiometer. All children showed right-hand preference according to the Edinburgh Handedness test (Oldfield, 1971).

2.2. Behavioral assessments

2.2.1. Wechsler Preschool and Primary School Scales of Intelligence (WPPSI)

In order to characterize the children's visuospatial reasoning and expressive language skills, two sub-tests from the WPPSI (Wechsler, 2003) were administered: block design and vocabulary. In the block design test the children are shown how to arrange red and white blocks to form a design and they have to build the same design. In more difficult sections the children are only shown the design in a figure and they have to build it. The scaled scores were used in the analyses to account for the age differences between children.

In the vocabulary test the children hear a word and they have to describe the meaning of that word. The scaled scores were used in the analyses. In both sub-tests the scaled scores have an average of 10 and a standard deviation of 3.

2.2.2. Sentence repetition

Verbal short-term memory ability was estimated using a task from NEPSY test (Korkman et al., 2008) where the children hear increasingly long sentences and have to try to repeat them as accurately as possible. The scaled scores (mean: 10, standard deviation: 3) were used in the analyses.

2.2.3. Letter knowledge

The children were asked to name each capital letter of the Finnish alphabet. Phonemic pronunciation was encouraged but letter names were also accepted. The task started with the initial letter of the child's own name and then proceeded in the order in which the letters are taught in school. The amount of correctly named letters (maximum of 29) was used in further analyses.

2.2.4. Phonological identification

In this computerized phonological processing task the children saw three objects on the screen and heard the name of each of the objects. Then a syllable was heard and the child had to point to the object that contained the syllable. In the last 10 items of the total of 20, the heard segment was a phoneme instead of a syllable. Number of correctly identified objects was used in the analyses.

2.2.5. Rapid automatized naming (RAN)

Pictures of five common objects had to be named as quickly and as accurately as possible. The objects were arranged in five rows each containing 15 objects. The task was audio-recorded and the time in seconds was calculated from the recording to be used in the analyses.

2.3. EEG procedure and stimuli

EEG was recorded in a sound-attenuated room while the children sat comfortably in an arm chair and watched a self-selected muted movie during the recording. The stimuli were presented in a passive oddball paradigm with 68.2% (835 trials) of the stimuli being standards, 10.6% frequency deviants, 10.6% duration deviants and 10.6% intensity deviants (130 trials for each). The inter-stimulus interval between the tones was 400 ms. The experiment lasted for 15 to 20 minutes depending on the number and length of breaks. The stimuli were presented through headphones (Sennheiser PX200) at equal loudness of approximately 70 dB(A), except for the intensity deviant. Standard stimuli were sinusoidal tones of 500 Hz in frequency and 200 ms in duration with 10 ms rise and fall times. Each of the deviants were otherwise the same as the standard stimuli, but differed in either frequency (425 Hz, 15 % change), duration (160 ms, 20 % change), or intensity (60 dB, 14 % change).

A second experiment using speech sounds was run during the same test session with counterbalanced order. The results from the speech sound experiment will be reported elsewhere.

2.4. EEG recording and pre-processing

EEG was recorded using 128 Ag-AgCl electrodes (Electrical Geodesics, Inc.) with Cz as the reference. The data were sampled at 1000 Hz, high-pass filtered at 0.1 Hz and low-pass filtered at 200 Hz. Impedances were aimed to be kept below 50 kΩ during the recording. The data quality was checked throughout the experiment and electrodes with poor data quality were adjusted.

BESA Research 5.3 was used for offline data processing. The EEG data were offline re-referenced to the average reference. The data were averaged according to each

stimulus type (only pre-deviant standards were included in the analyses). Epoch length was from -100 ms (pre-stimulus baseline) to 500 ms. Artifact detection criteria were 120 μV for amplitude fluctuations within the whole epoch, and 75 μV for fast transient artifacts between adjacent time points. Channels showing continuously noisy data were interpolated using the spherical spline method (order of splines: 4; maximal degree of Legendre polynomials: 50; approximation parameter Lambda: 1.0e−005). After artifact rejection the range of accepted number of epochs was 83-119 for the responses to each of the deviant stimuli and 270-387 for the response to the pre-deviant standard stimulus, and 0.6 bad channels on average (range 0–4) were interpolated for the control children. For the at-risk children there were 72-107 trials left for the responses to each of the deviant stimuli and 229 – 334 trials left for the response to the standard stimulus, and 0.4 (range 0 – 1) bad channels were interpolated on average. There were no statistically significant differences between groups in the trial numbers (all t-values < 1.380 and p-values > 0.178). A lowpass filter of 30 Hz (zero-phase, 24 dB/octave) was applied after averaging.

2.5. Data analysis

Behavioral test scores were compared between groups using non-parametric Mann-Whitney tests due to the small sample size of the at-risk children. Correlations between ERP and behavioral measures were examined across the two groups using Pearson correlation coefficients.

In order to examine statistical differences between the responses to the deviant and standard stimuli the averaged ERPs were exported to BESA Statistics 1.0. The response to each of the deviant stimuli was compared to the combined average of the response to the standard stimuli occurring immediately prior to each deviant stimulus. The comparison was made using bootstrap statistics with channel and time-point clustering. The amount of

permutations was set to 1000 for each contrast and the channel cluster limit was set to 4 cm. Permutation testing is a non-parametric method that uses the random partitioning of the groups/conditions in order to estimate the distribution of the effect of interest. By comparing the original test statistic with the permutation distribution it is possible to calculate the p-value for the effect (for further information on the permutation testing, see Bullmore et al., 1999; Ernst, 2004; Maris & Oostenveld, 2007).

Source localization was carried out in BESA Research 5.3 to reveal the approximate brain areas responsible for the group differences. Bone thickness of 5 mm and conductivity of 0.018 were used, the estimates for 6-year-old children given in the BESA software. Other tissue thicknesses and conductivities were kept at the level of adults. Equivalent current dipole models were examined first and CLARA (Classic LORETA Recursively Applied; Hoechstetter et al., 2010; Hämäläinen et al., 2011) distributed source models were used as the confirmation method. Analyses were carried out for time windows showing group differences. The source models were based on information from all of the recording channels.

3. Results

3.1. Behavioral assessments

Children at risk for dyslexia showed lower scores in block design, vocabulary, and sentence repetition compared to control children. Additionally, children at risk for dyslexia showed a trend towards lower scores in letter knowledge (Table 1). No group differences were found in the syllable and phoneme identification task. These results indicate that the children with a family history of dyslexia had a wide range of risk factors for learning difficulties in addition to the family history of reading problems.

Table 1. Age and group statistics for behavioral measures and group differences tested with Mann-Whitney U test.

	Controls (N = 26)	Risks (N = 11)	Group difference
Age at behavioral testing	5.2 (0.56)	5.4 (0.77)	U=105, Z=-1.26, ns
Block design (standard score)	9.92 (3.60)	6.55 (2.73)	U=58, Z=-2.95**
Vocabulary (standard score)	9.96 (1.90)	6.82 (1.54)	U=28, Z=-3.805***
Sentence repetition (standard score)	11.27 (3.04)	7.60 (3.20)§	U=71, Z=-2.09*
Letter knowledge (max. 29)	17.73 (10.51)	12.36 (10.84)	U=90, Z=-1.77+
Phonological processing (identification)	13.73 (10.51)	11.55 (3.11)	U=98.5, Z=-1.48, ns
RAN, time in seconds	79.84 (16.28), N=25	89.91 (27.29)	U=94, Z=-1.50, ns

§N=10, +$p<0.083$, *$p<0.05$, **$p<0.01$, ***$p<0.001$

3.2. Event-related potentials in the control group

Figure 1 shows the grand average response to the standard stimuli with a frontocentrally positive deflection at 102 ms followed by two negative deflections at 235 ms and 353 ms (latencies from Fz channel), corresponding to P1, N2/N250 and most likely N4/N450 responses reported in previous literature (e.g., Ceponiene et al., 2002; Lovio et al., 2010; Ponton et al., 2000). All deflections showed a reversal of the voltage into opposite values near the mastoid areas (see Figure 2).

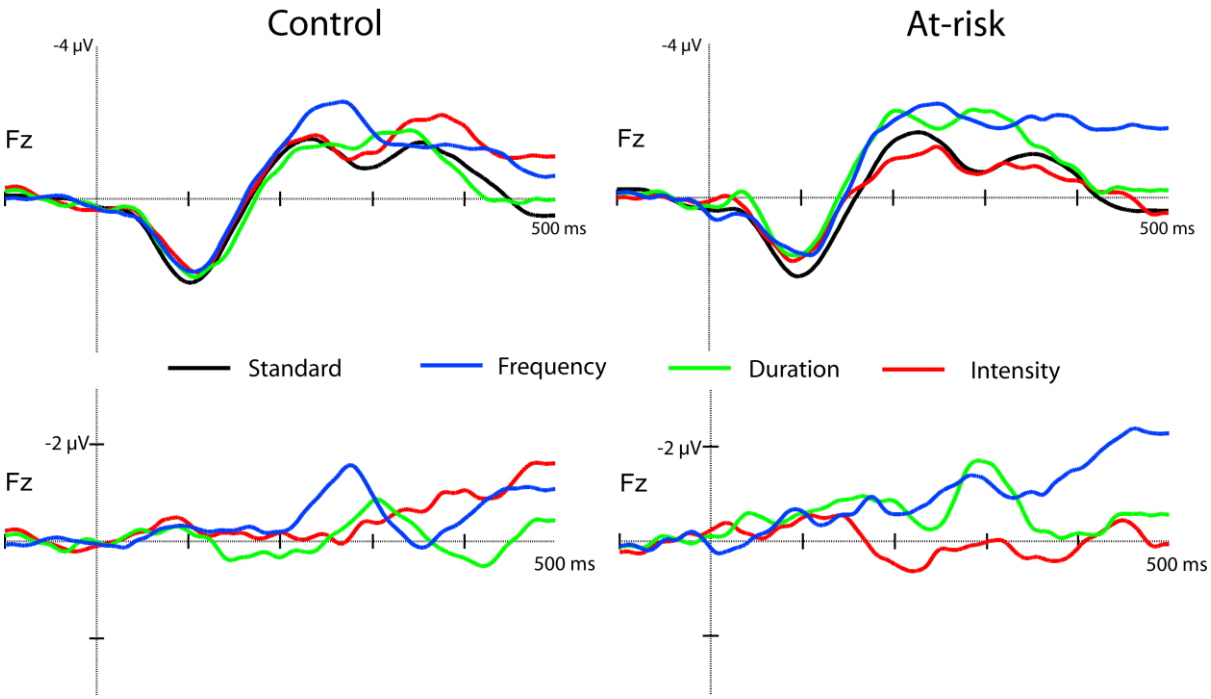

Figure 1. Above: Response to the pre-deviant standard (black), frequency (blue), duration (green) and intensity (red) changes at Fz channel in control children (N = 26) (right) and children at risk for dyslexia (N = 11) (left). Below: Difference waveforms (response to deviant stimulus minus response to standard stimulus) of the frequency, duration and intensity deviant stimuli (blue, green and red lines, respectively) in control children (N = 26) (right) and children at risk for dyslexia (N = 11) (left).

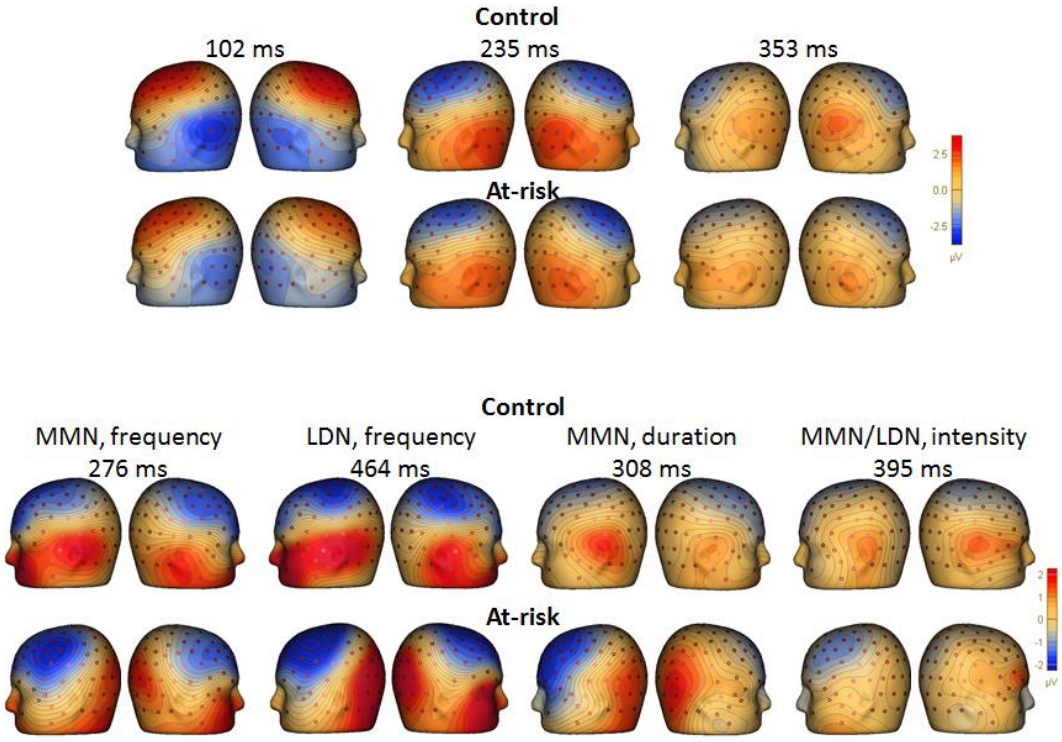

Figure 2. Above: The pre-deviant standard response topographies of the three major deflections, P1 (102 ms), N250 (235 ms) and N350 (353 ms), in control children (N = 26; Row 1) and children at risk for dyslexia (N = 11; Row 2). Below: Topographic distribution of the difference wave voltages in response to the frequency, duration and intensity deviations at the mismatch negativity (MMN) and late discriminative negativity (LDN) time windows in control children (3rd row) and children at risk for dyslexia (4th row). Blue represents negative voltages, red positive voltages.

The responses to the frequency, duration, and intensity changes were examined from the difference waves. For the frequency change, as shown in Figure 1, the grand average at Fz channel shows a clear negative deflection at 276 ms followed by another negative wave at 470 ms. The topography of both responses had frontocentral negative voltages and positive voltages near the mastoid areas (Figure 2). To examine statistically significant differences between the responses to the standard stimuli and the frequency deviant stimuli, permutation

testing with data clustering revealed one channel cluster that differed between the responses (Figure 3). As can be seen from Figure 3, the cluster had frontocentral negative voltages that became positive at both the left and right temporal and mastoid channels at 115-500 ms ($p < 0.0001$). For the duration change the waveform peaked at 307 ms with frontocentral negative voltage and positive voltage near the mastoid areas (Figure 2). This was followed by a small frontally positive deflection at 422 ms and finally a second frontocentrally negative deflection at 478 ms. As shown in Figure 3, permutation testing revealed deviant larger than standard frontocentral channel cluster with voltage polarity reversal at left temporal and mastoid channels at 258-366 ms ($p < 0.006$). The difference wave for the intensity change did not show any clear peak. Instead, a slow frontocentral negative drift was observed starting around 290 ms (Figure 1). This drift also had positive voltages near the mastoid areas. Permutation testing revealed a frontocentral channel cluster that showed statistically significant differences between the responses to the standard and intensity deviant stimuli at 365-500 ms ($p<0.009$) (Figure 3).

3.3. Event-related potentials in the risk group

Two channel clusters with statistically significant differences between the responses to the frequency change and standard stimulus were found (Figure 3). The first cluster had larger negative voltages at frontocentral electrodes in a long time window (132-500 ms; $p<0.00001$). The second cluster had a drift towards positive voltages in the response to the frequency deviant compared to the response to the standard stimulus at posterior channels at 62-500 ms ($p<0.002$). For the duration deviant, two statistically significant clusters were found (Figure 3): the responses differed at frontocentral sites at 256-315 ms ($p<0.016$) where response to the duration change had larger negative voltages than the response to the standard. The second cluster was found at the right mastoid channels where the response to

the frequency change had more positive voltages than the response to the standard at 274 – 500 ms ($p<0.003$). No statistically significant clusters were found when comparing the responses to the intensity change and the standard stimulus.

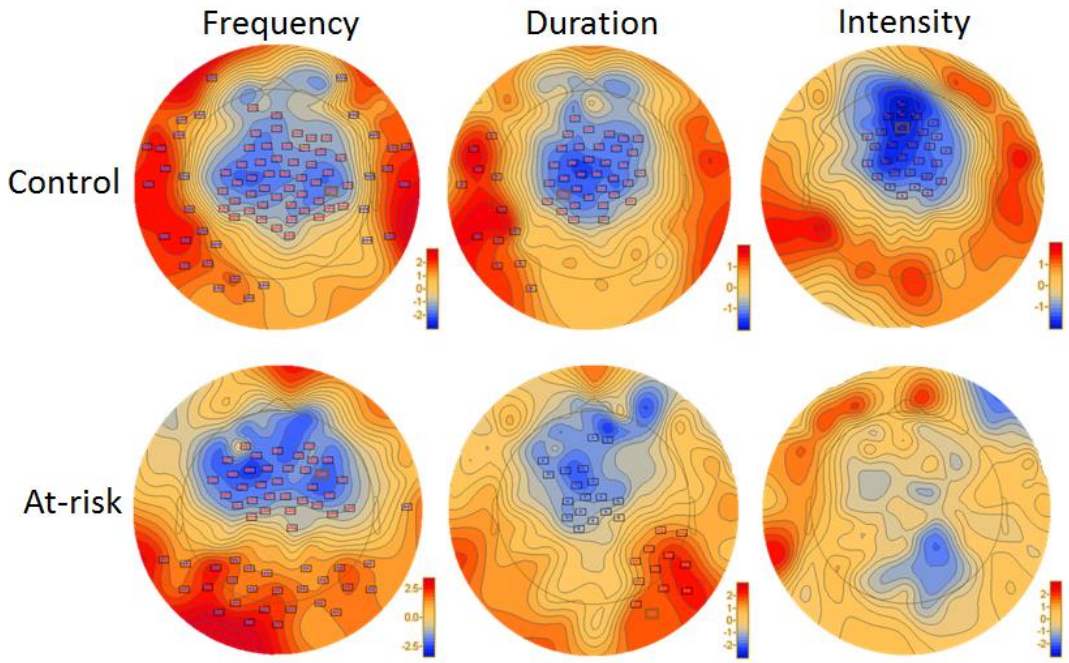

Figure 3. Difference topographies (response to deviant stimulus minus standard stimulus) for frequency changes at 115-500 ms (left), duration changes at 258-366 ms (middle) and intensity changes at 365-500 ms (right) in the control goup (N = 26) and for frequency changes at 62-500 ms (left), duration changes at 256-500 ms (middle) and intensity changes at 395 ms (right) in children at risk for dyslexia (N = 11). The marked channels indicate statistical clusters that differ between the responses to the standard and deviant stimuli. Blue signifies negative amplitudes and red signifies positive amplitudes. The units are in µV.

3.4. Group comparisons

3.4.1. Response to the standard stimulus

Children at risk for dyslexia showed a statistically significant shift towards negative amplitudes at the frontocentral areas at 107–215 ms, encompassing the offset of P1 and onset

of N250 responses ($p<0.04$) compared to the control children (Figure 4). In order to examine the approximate brain area responsible for the group difference, the ERPs of the control children to the standard stimulus were subtracted from those of the at-risk children and the 107 – 215 ms time window was used in source localization. As seen from Figure 5, the group difference originated very close to the primary auditory cortices in the left and right hemispheres. This result was calculated using both equivalent current dipoles and CLARA solutions, and both methods converged on the same locations. Dipole locations were also examined separately for each group and the dipole locations between groups were close to each other. Thus the localization from the difference waveform was justified.

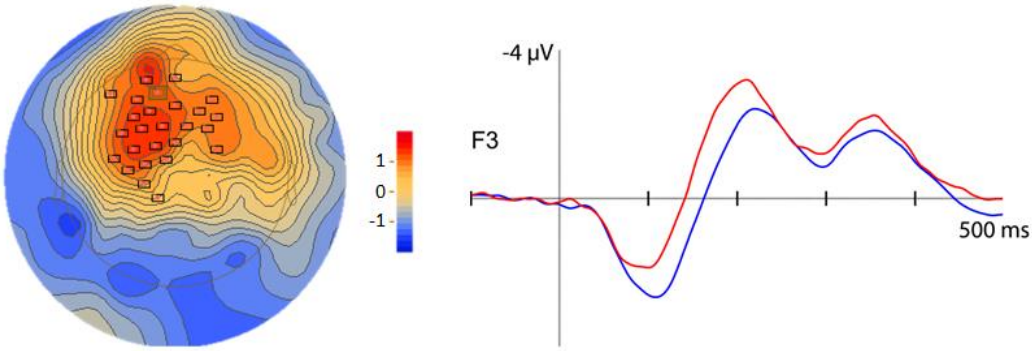

Figure 4. Left: Group difference topography between the control children (N = 26) and children at risk for dyslexia (N = 11) for the standard stimulus response at 107-215 ms. The marked channels (rectangles) form statistical clusters that differ between the groups. Blue signifies negative amplitudes and red signifies positive amplitudes. The units are in µV. Right: Representative channel (F3) of the group difference showing the ERP waveform of the control children (blue) and children at risk for dyslexia (red). Negativity is plotted up (scale: 4 µV). Horizontal tick marks represent 100 ms intervals.

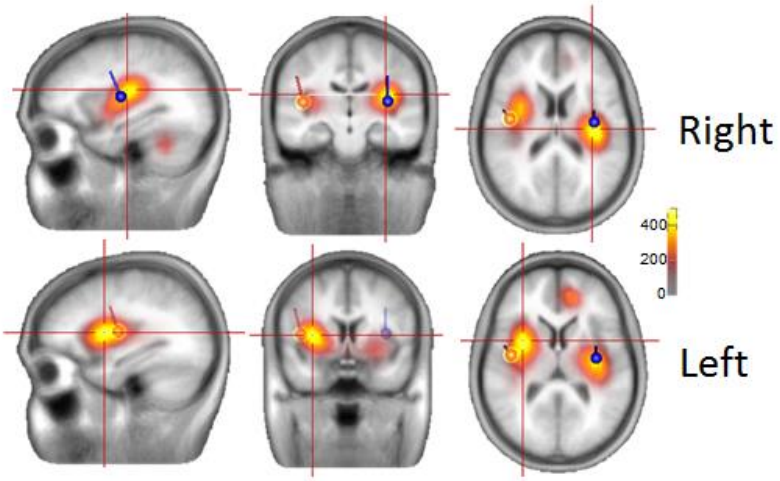

Figure 5. Source localization of the P1-N250 group difference (response of the control children minus response of the at-risk children) with residual variance of 4.6 % for left and right auditory cortex dipoles. The CLARA solution shows converging locations to those of the dipole model.

3.4.2. Response to the standard stimulus and correlations to behavior

The amplitude values were averaged from the 107-215 ms time window showing the group difference. This average amplitude was correlated with behavioral measures in each channel across the two groups. The block design standard score showed statistically significant association to fronto-central and right mastoid area amplitudes (see Figure 6). Vocabulary scores showed statistically significant correlations on three channels only. The most consistent associations were found between the ERP amplitude and letter knowledge, showing central and left temporal area correlations. These correlations remained statistically significant even after controlling for block design or when examining only the control children (e.g., channel Cz, $r=0.488$, $p<0.003$ without block design controlled for across all children; $r=0.524$, $p<0.008$ with block design controlled for; $r=0.550$, $p<0.005$ across control children only). The phonological identification task had statistically significant correlations with mostly central ERP amplitudes, which also remained after controlling for block design

or when examining control group only (e.g., channel 30, r=0.429, p<0.009 without block design controlled for across all children; r=0.408, p<0.044 with block design controlled for; r=0.424, p<0.032 across control children only). The correlations suggest that despite the group difference in block design, the difference in ERP is due to phonological and reading-related abilities. Rapid naming showed significant correlations in seven channels located near occipital areas. Sentence repetition showed significant correlations in 17 channels located at the frontal and parietal areas. Examination of the scatterplots reveals that the correlations are not due to variation in only one of the groups (see Figure 7). If a threshold for multiple correlations is used (at least six contiguous electrodes show significant correlation) then only block design, phonological identification and letter knowledge remain correlated with the ERP amplitude.

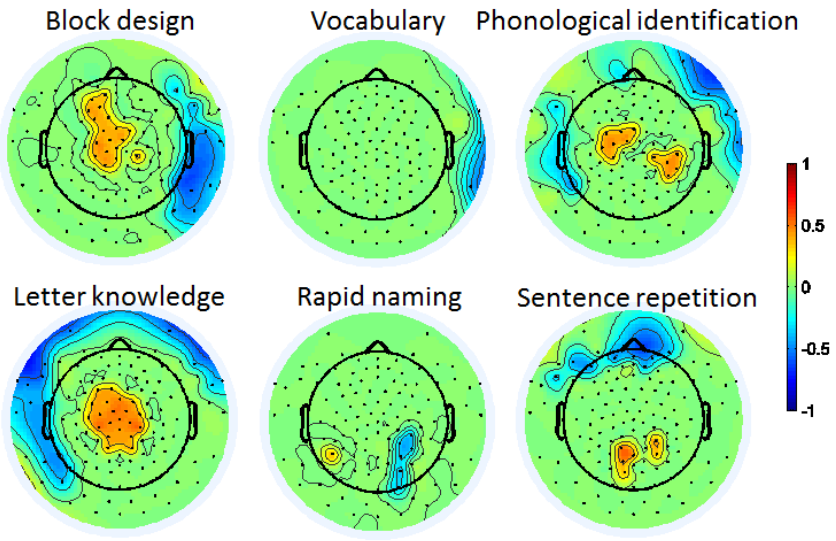

Figure 6. Significant correlation coefficients ($p < 0.05$) between ERP amplitude at 107-215 ms to the standard sound and behavioral test scores across all children (N = 37). All non-significant correlations have been changed to a value of zero and are therefore represented by the green color.

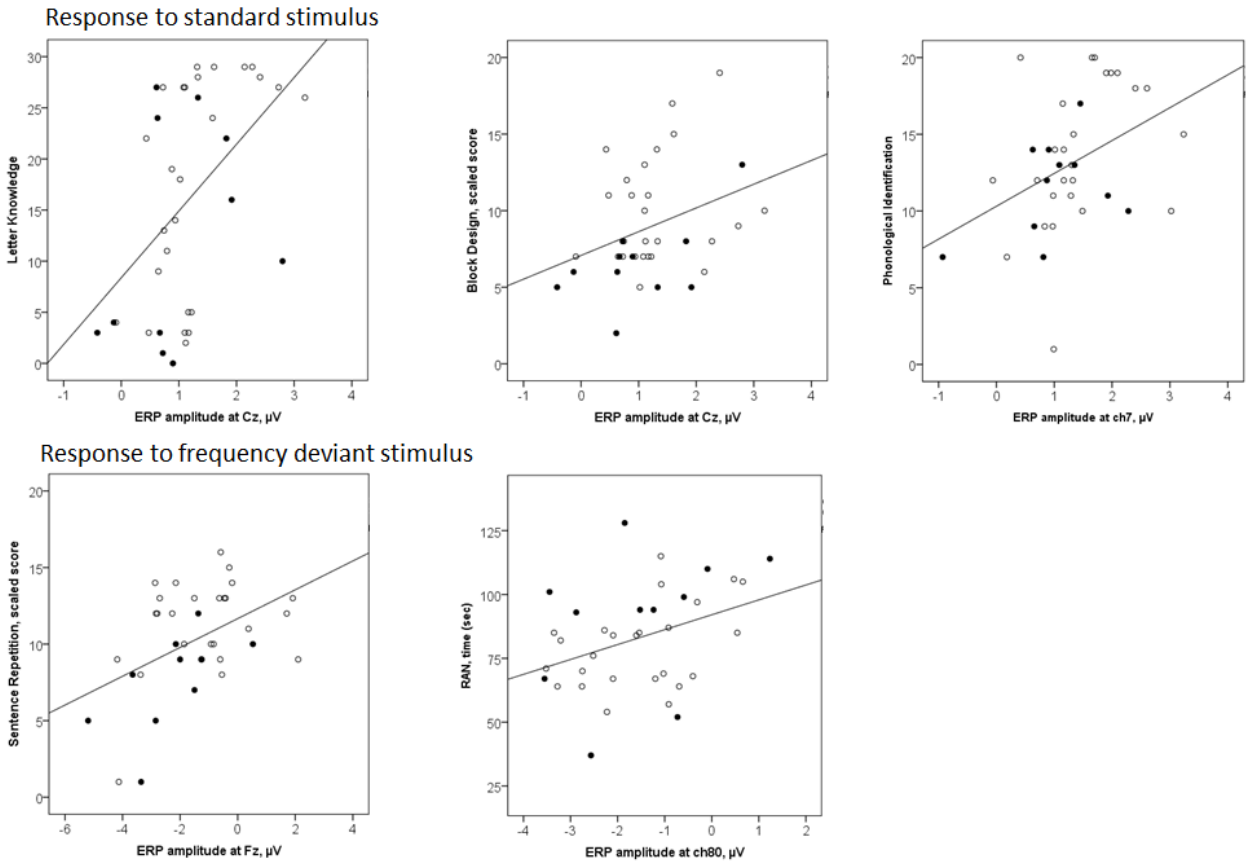

Figure 7. Example scatterplots of the correlations between the ERP amplitudes and behavioral test scores at representative electrodes. The top row includes scatterplots between the ERP amplitude to the standard stimulus and behavioral measures and the bottom row includes scatterplots between the ERP amplitude to the frequency deviant stimulus and behavioral measures. The filled black circles represent children at risk for dyslexia (N = 11) and the open black circles control children (N = 26).

3.4.3. Responses to the deviant stimuli

Children at risk for dyslexia showed a statistically significant larger positive deflection in the difference wave for the frequency deviant stimulus at the occipital channels than control children starting at 358 ms and lasting until the end of the 500 ms epoch ($p<0.009$) (Figure 8). No group differences were observed for the duration or intensity deviant stimuli.

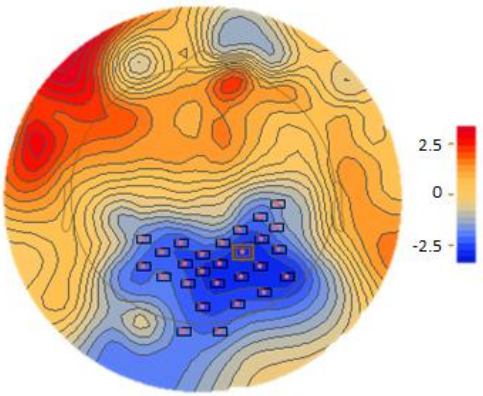

Figure 8. Group differences at 358-500 ms between control children (N = 26) and children at risk for dyslexia (N = 11) in responses to the frequency change (difference wave measure). The difference voltage map between control and at-risk children is shown. The marked channels (rectangles) form statistical clusters that differ between the groups. Blue signifies negative amplitudes and red signifies positive amplitudes. The units are in μV.

3.4.4. Response to the frequency deviant stimulus and correlations to behavior

ERP amplitude values were averaged across the time window showing the group difference in response to the frequency change in the difference wave (358 – 500 ms). As can be seen from Figures 7 and 9, block design scores showed statistically significant correlations in three separate channels only, but vocabulary, phonological identification, and letter knowledge scores showed significant correlations in five channels. The most consistent correlations were found between the response to the frequency change and the sentence repetition scores. The correlation was significant at the frontal and parietal channels. This correlation pattern survived when block design performance was controlled for (e.g., channel 22, $r=0.541$, $p<0.002$ without block design controlled for across all children; $r=0.592$, $p<0.001$ with block design controlled for; $r=0.566$, $p<0.004$ across control children only). Also, RAN time correlated with the ERP amplitude at the right central channel and at some frontal channels. Nine of the fifteen significant correlations survived after controlling for the performance in

the block design task (e.g., channel 87, r=0.406, p<0.015 without block design controlled for; r=0.372, p<0.029 with block design controlled for; r=0.480, p<0.016 across control children only). If a threshold for multiple correlations is used (at least six contiguous electrodes show significant correlation) then only sentence repetition and rapid naming remain correlated with the ERP amplitude.

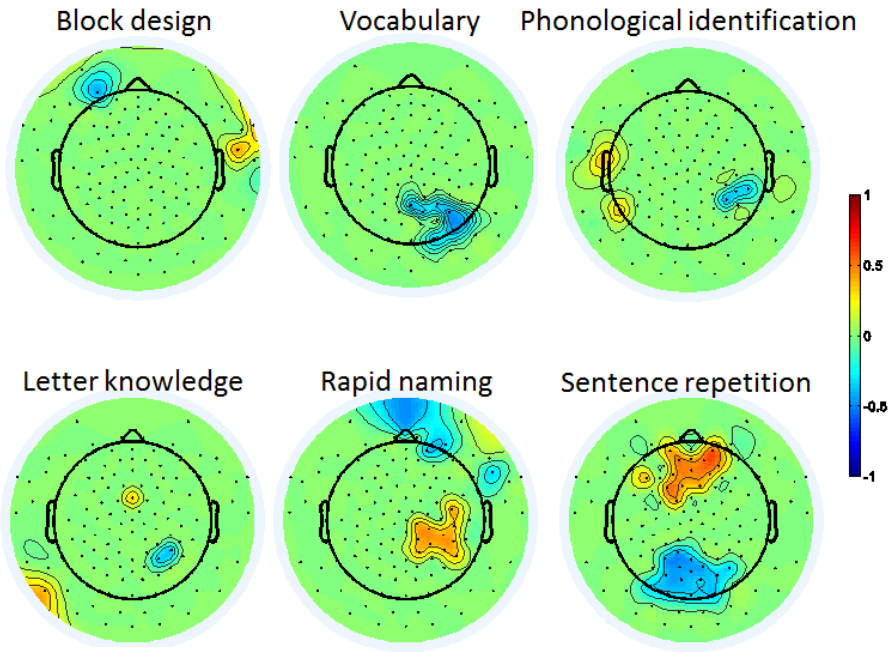

Figure 9. Significant correlations ($p < 0.05$) between ERP amplitude at 365-500 ms to the sound frequency change (difference wave) and behavioral test scores across all children (N = 37). All non-significant correlations have been changed to a value of zero and are therefore represented by the green color.

4. Discussion

The current study examined the auditory processing abilities of preschool children with and without multiple risk factors for dyslexia. These multiple risk factors were evident in the behavioral test results showing generally lower visuospatial reasoning, vocabulary, verbal short-term memory abilities, and letter knowledge in the family risk group compared to

control children. However, it should be noted that rapid automatic naming and phonological skills did not show group differences, and for letter knowledge the difference was only marginally significant. Auditory ERPs showed a group difference in non-specific automatic processing of sounds at a relatively early time window (107–215 ms). Correlation analyses with pre-reading skills (letter knowledge and phonological identification) corroborated that the group difference was linked to reading related skills. Additionally, the children with family risk showed enhanced late discriminative negativity (LDN) to the frequency change and this LDN amplitude was correlated particularly with verbal short-term memory. No significant group differences in ERPs were found for duration or intensity changes in sounds.

In general, the preschool children showed the expected P1-N250 response to the standard stimuli with frontocentral voltage distributions (Albrecht et al., 2000; Ceponiene et al., 1998; Ponton et al., 2000; Sharma et al., 1997; Sussman et al., 2008). Additionally, a negative frontocentral peak was observed at 350 ms latency. This response is similar to that found in previous studies and called N4 or N450 (Ceponiene et al., 2001; Lovio et al., 2010). The control children also showed an MMN response to the frequency and duration changes and a later negative shift for intensity changes. The frontocentral distribution of MMN was similar to that found in adults, but the latency was slightly longer, observed to peak after 250 ms (Giard et al., 1995; Näätänen et al., 2010; Rosburg, 2003). The response to the intensity change showed a clearly different pattern of change detection response. The response was late (starting at 365 ms) and suggests that it could be late discriminative negativity instead of mismatch negativity. The response to the intensity change was also clearly later than the MMN response typically reported in adults (Giard et al., 1995; Näätänen et al., 2004; Rosburg, 2003). There are two possibilities for the different latencies elicited by the different deviant stimuli. First, it is possible that afferent activation in response to a frequency change could have caused the earlier latency for that deviant stimulus compared to the other deviant

stimuli (e.g., Lohvansuu et al., 2013). Second, the frequency and duration changes elicited a different kind of change detection process compared to the intensity change. This would be supported by the finding that the waveform of the frequency and duration changes showed a second later negativity at 470 ms and 438 ms after deviancy onset, respectively, with a frontocentral distribution. This second negativity corresponds to LDN reported in previous studies (Ceponiene et al.,2004; Korpilahti et al., 2001; Schulte-Körne et al., 1998). The late latency of the response to the intensity change could thus reflect LDN and not MMN. This would be supported by earlier findings showing no MMN response to intensity changes in children (Stefanics et al., 2011; Sussman & Steinschneider, 2011), although in one study similar slow late negativity for intensity decrements to that of the current study is observable in the waveforms (Sussman & Steinschneider, 2011).

Preschool children at familial risk for dyslexia showed basic auditory processing differences to age-matched controls. They showed a shift towards negative amplitudes at P1 offset and N250 onset compared to controls and an enhanced LDN for frequency change. The larger negative onset of the N250 is in line with a previous study of kindergarten children with later confirmed dyslexia (Hämäläinen et al., 2013a). The negative shift caused the P1 to become smaller in the at-risk children than in controls and in that sense the result is in line with the findings of Lovio and colleagues (2010) regarding smaller P1 response in children at risk for dyslexia, but they did not find a longer lasting amplitude shift. The topography of the group difference had frontocentral distribution and source locations clearly in the left and right auditory cortex. The difference started already at 107 ms and lasted until 215 ms. This time window will develop into N1-P2 responses later in life (Albrecht et al., 2000; Ponton et al., 2000). It remains unclear what this early group difference specifically signifies besides differences in auditory cortex functions.

The correlations between the ERP amplitude to the standard stimulus and behavioral measures suggest that differences in the functioning of the auditory cortices are related particularly to letter knowledge and phonological identification. This makes sense from the point of view that phonological awareness is at least to some extent dependent on speech perception abilities. Speech sounds need to be heard correctly for efficient formation of speech sound representations, which is a prerequisite in performing at an optimal level in phonological awareness tasks. Further, the speech information has also to be retained in verbal short-term memory and operations executed based on the task requirements (e.g., Vellutino et al., 2004). Letter knowledge in turn utilizes phonological representations of the phonemes in order to combine information about the speech sounds with written symbols (e.g., Vellutino et al., 2004). Therefore, the performance in the letter knowledge task is also partly dependent on speech perception. It should be noted that the letter knowledge task in the current study could be performed by using either letter sounds or letter names and therefore the contribution of phonological awareness and letter name knowledge to this measure could vary between the groups. Nevertheless, the performance in these two tasks measuring pre-reading skills correlated with the auditory ERP amplitude.

Group differences also emerged for frequency change processing. The group difference started at 358 ms, indicating that the MMN response per se, occurring at an earlier time window starting from 115 ms, was intact in children at risk for dyslexia whereas the LDN showed abnormally large amplitude. The latency of this group difference is in line with a previous study of Maurer and colleagues (2003) that showed attenuated LDN amplitudes starting at 457 ms in kindergarten children at risk for dyslexia compared to controls. They also found group differences at an earlier time window, but the polarity of the response was positive at fronto-central channels in their study (Maurer et al., 2003). Interestingly, MMN and LDN responses to speech sounds in individuals with dyslexia have been linked to rare

variants of dyslexia susceptibility genes (Czamara et al., 2011; Roeske et al., 2011). Thus it is possible that the atypical LDN response in the present study is linked to the genetic differences between the children at risk for dyslexia and control children. Although not all of the at-risk children will later develop dyslexia, based on recent studies (Leppänen et al., 2010; Neuhoff et al., 2012; Plakas et al., 2012) it is still possible that the LDN difference can be associated with genes increasing the chance of developing dyslexia. For example, Neuhoff and colleagues (2012) showed that both children with dyslexia and their non-affected siblings showed attenuated LDN compared to unrelated controls with no family history of dyslexia. Similarly, studies by Plakas and colleagues (2012) and Leppänen and colleagues (2010) suggest that the risk for dyslexia in itself is sufficient to cause differences in auditory processing and not only the actual reading outcome at school age.

LDN amplitude correlated most strongly with sentence repetition, a measure of verbal short-term memory. This was in contrast to the correlations found at the earlier P1-N250 time window where phonological and letter knowledge skills correlated significantly but sentence repetition showed somewhat less strong association. This pattern of correlations at these two different time windows (P1-N250 and LDN) could reflect the time course of different cognitive processes in which ERPs generated in the auditory cortices after 100 ms share variance with speech perception related skills, whereas ERPs at later time windows, beyond 350 ms, are related to more complex cognitive functions such as short-term memory.

There are previous studies examining the auditory ERP responses of 6.5-year-old kindergarten children at-risk for dyslexia who were at school age tested for their reading skills. These studies have shown those at-risk children who became dyslexics at school-age to differ from at-risk children who became typical readers at school in their ERP responses and that these ERP responses measured in 6.5 year-olds are associated with school-age reading skills (Hämäläinen et al., 2013a; Maurer et al., 2003; 2009). In contrast, children at risk for

dyslexia whose ERPs were measured at 41 months seem to differ from children with no risk for dyslexia (controls) regardless of the later reading outcome of the at-risk children, i.e. both at-risk children with school-age dyslexia and at-risk children with typical school-age reading skills differed from typically reading control children with no family risk for dyslexia (Plakas et al., 2012). Similar findings were reported for at-risk infants whose ERPs were measured at birth and whose reading skills were tested at the end of second grade: Robust differences in ERPs were found between children at risk for dyslexia and the controls regardless of reading outcome (Leppänen et al., 2010). However, in that study the at-risk children with school-age dyslexia and the at-risk children with typical school-age reading skills also differed from each other in their ERP responses. Thus it seems that ERPs to basic auditory processing measured at early ages show differences between at-risk children and controls regardless of their later reading outcome, whereas ERPs measured just prior to school entry (6.5-years) reflect more clearly differences between at-risk children who develop dyslexia and those who do not. It is possible that also at the age of 5.5 years (the current study) most children with a risk for dyslexia show altered auditory ERPs and later on protective factors start to take effect for those children who end up becoming typical readers.

It has been suggested that the LDN response reflects processes of letter-speech sound integration, attention, long-term memory transfer, or further cognitive processing of the sound change (Ceponiene et al., 2004; Cheour et al., 2001; Froyen et al., 2009; Shestakova et al., 2003; Zachau et al., 2005). In the present study, no letter-speech sound integration was possible in the experimental paradigm, and the sine-wave tones would be unlikely to activate long-term memory representations or to require the storage of complex rules. Thus it is likely that the LDN in the present study reflects attentional processes or further preattentive processing of the sound change.

Interestingly in the present study the processing of sound duration was found to be intact in the children at risk for dyslexia. Previous studies have rather consistently shown group differences between individuals with dyslexia and typical readers with large effect sizes (e.g., Corbera et al., 2006; Huttunen et al., 2007; for a review, see Hämäläinen et al., 2013b). The effect size of the group difference for duration discrimination has been found to be larger than that for frequency discrimination (Hämäläinen et al., 2013b) and therefore the relatively small group size should not be the cause for the lack of group difference in duration processing. Other factors are likely to have affected how this study's results differed compared to previous studies. Such factors could be stimulus presentation rate, size of the duration change, or the context of presentation together with frequency and intensity changes. The role of these other factors is, however, unclear.

We found no significant group difference in the amplitude of the LDN to the intensity change. However, the control children showed a difference in processing between the standard and intensity deviant stimuli while responses of the children at risk for dyslexia did not differentiate between the standard and deviant stimuli. The lack of group difference in this case could indicate large variability in the LDN amplitude and therefore this finding should be interpreted with caution. If this finding is interpreted as a lack of group difference in processing of intensity change it would be well in line with previous studies. Although intensity perception in dyslexia has not been studied as rigorously as, for example, frequency perception, almost all previous studies have not reported group differences in intensity discrimination or detection between individuals with dyslexia and typical readers (e.g., Hämäläinen et al., 2013b; Kujala et al. 2006; Richardson et al., 2004).

In summary, we found differences in ERPs most likely originating from the auditory cortices between 5.5-year-old children with multiple risk factors for dyslexia and age-matched controls. We also found differences between groups in the later processing stage

(late discriminative negativity) of frequency change, but not of duration or intensity change. The results support the hypothesis that auditory processing differences are present before reading instruction begins and that these differences are present in many of the at-risk children indicating a role of a risk factor for impaired reading development.

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