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An extensive pattern of atypical neural speech-sound discrimination in newborns at risk of dyslexia

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HIGHLIGHTS

- Familial dyslexia risk is associated with deficient speech-sound processing already at birth.
- Mismatch responses to speech-sound changes were absent, diminished or atypical in at-risk newborns.
- Speech-processing deficits at birth might serve as early neural markers of language disorders.

ABSTRACT

Objective: Identifying early signs of developmental dyslexia, associated with deficient speech-sound processing, is paramount to establish early interventions. We aimed to find early speech-sound processing deficiencies in dyslexia, expecting diminished and atypically lateralized event-related potentials (ERP) and mismatch responses (MMR) in newborns at dyslexia risk.
Methods: ERPs were recorded to a pseudoword and its variants (vowel-duration, vowel-identity, and syllable-frequency changes) from 88 newborns at high or no familial risk. The response significance was tested, and group, laterality, and frontality effects were assessed with repeated-measures ANOVA.
Results: An early positive and right-lateralized ERP component was elicited by standard pseudowords in both groups, the response amplitude not differing between groups. Early negative MMRs were absent in the at-risk group, and MMRs to duration changes diminished compared to controls. MMRs to vowel changes had significant laterality × group interactions resulting from right-lateralized MMRs in controls.
Conclusions: The MMRs of high-risk infants were absent or diminished, and morphologically atypical, suggesting atypical neural speech-sound discrimination.
Significance: This atypical neural basis for speech discrimination may contribute to impaired language development, potentially leading to future reading problems.

1. Introduction

Difficulties in learning to read and write can lead to severe problems in social and academic development. Developmental dyslexia, affecting 4–17% of the population (Elliott and Grigorenko, 2014), is a learning impairment specific to reading and writing despite affected individuals' otherwise intact cognitive abilities. The underlying cause for dyslexia is partially genetic, i.e., the genetic variation accounts for at least 50% (DeFries and Fulker, 1985) or even up to 70–80% (Kere, 2014) of the variation in reading and related difficulties in dyslexic individuals. Several dyslexia susceptibility genes have already been identified (Kere, 2014). Dyslexia often occurs in combination with other developmental disorders, such as developmental language disorder (DLD; former: specific language impairment, SLI). Both disorders were suggested to be based on similar core mechanisms (Bishop and Snowling,

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2004), specifically phonological processing deficits and processing of time-varying acoustic events (Chandrasekaran and Kraus, 2012), and show an overlap in electrophysiological (Choudhury and Benasich, 2011), behavioral (de Wit et al., 2017), and genetic (Newbury et al., 2011) components.

Dyslexia can be diagnosed at school age, when children start to exhibit difficulties in reading-skill acquisition. If children at high risk of dyslexia could be identified and treated prior to school onset, social and academic outcomes of these children could be drastically improved (Gabrieli, 2009). A prerequisite for designing early interventions is to identify reliable markers of the deficient neural processes that may underlie dyslexia.

One of the current leading theories on dyslexia suggests that the majority of affected individuals have a phonological processing impairment, proposed to be based on a deficient formation, storage and/or retrieval of speech-sound representations in the brain (Ramus, 2001; Ramus and Szenkovits, 2008). As learning to read requires fast and accurate mapping of letters to their corresponding speech sounds in the brain, abnormal development of the speech-sound representations, or access to them, would result in inaccurate or slow assembly/access of the neural network required for fluent reading (Ramus and Szenkovits, 2008). The deficiency in the development of speech-sound representations reflected in neurophysiological responses could serve as a neural predictor for future reading problems in dyslexia (Kujala, 2007). Whereas these responses cannot yet be used in diagnostics at the individual level, this suggestion is supported by findings showing that at group level, some of these response are associated with future reading skills (for a review, see Volkmer and Schulte-Körne, 2018).

1.1. Neurophysiological means to evaluate speech-sound processing during early development

Neural speech-sound representations can be probed with the mismatch negativity (MMN; Näätänen et al., 2007), an event-related potential (ERP) component elicited at 150–250 ms after the onset of rare deviants presented among frequent standard stimuli (Näätänen, 2001). Its response amplitude is greater to large than small sound changes and correlates with behavioral change detection performance, thus reflecting stimulus discrimination accuracy (Kujala and Näätänen, 2010). The MMN has been widely used to study speech-sound processing in healthy and clinical populations (Näätänen et al., 2011). In developmental dyslexia, diminished MMN amplitudes have been found to speech- and non-speech-sound changes (Kujala and Näätänen, 2001; Kujala, 2007; Hämäläinen et al., 2013), suggesting an impairment of neural sound discrimination in dyslexia, consistent with the phonological deficit hypothesis.

Being elicited even in inattentive participants (Winkler, 2007), MMN is a feasible tool to investigate auditory processing in early infancy, even at (Alho et al., 1990) or before birth (Huotilainen et al., 2005). The infant equivalent of MMN, the mismatch response (MMR; a term also used hereafter) is often positive in polarity (Trainor, 2012) which has been suggested to arise from various factors (Kushnerenko et al., 2013). For example, positive MMRs could indicate neural immaturity and negative MMRs maturity (e.g., Mueller et al., 2012; cf. see also Leppänen et al., 2004) since, e.g., positive MMRs are most pronounced in young infants and get weaker with age (Morr et al., 2002; He et al., 2007, 2009), and negative MMRs are least pronounced in young infants and get stronger during the first year of life (Kushnerenko et al., 2002; Trainor et al., 2003; He et al., 2007, 2009). Infant MMRs of opposite polarities might reflect distinct neural processes, as they can be separated by using different filter settings (Trainor et al., 2003; He et al., 2007), differ in their scalp distribution (He et al., 2007), and can co-occur and overlap in time (Leppänen et al., 1997). Even though the exact mechanism of infant MMR generation remains unclear, regardless of response polarity, infant MMRs were suggested to be indices of auditory discrimination (Leppänen et al., 1997; Trainor et al., 2003).

Infant MMR studies have shed light on the development of early auditory abilities. For example, they have shown that already at birth, infants can discriminate duration and frequency differences (Alho et al., 1990; Leppänen et al., 1997; Čeponiene et al., 2002). They are even able to process complex sound relationships, like rules in sound patterns and musical chords (Virtala et al., 2013; Háden et al., 2015). Along with these abilities, newborns possess necessary prerequisites for language processing and, indeed, they can also neurally differentiate changes in language-relevant stimuli, such as changes in vowels, consonants, and their durations in syllables or pseudowords (Cheour-Luhtanen et al., 1995; Leppänen et al., 1999; Kushnerenko et al., 2001; Partanen et al., 2013).

1.2. Speech-sound processing in infants at familial risk of dyslexia

Familial risk of dyslexia can influence the elicitation of MMRs. Six- and two-month olds at risk of dyslexia were found to have smaller or absent MMRs than control infants at no risk of dyslexia to consonant duration changes in a pseudoword or changes in consonant-vowel-consonant (CVC) syllables, respectively (Leppänen et al., 2002; van Leeuwen et al., 2008). In newborns at risk of dyslexia, ERPs were larger than in control newborns to shorter vowels in syllables, presented as deviant stimuli among syllables with long vowels (Leppänen et al., 1999). This rather unexpected finding might result from differences in the obligatory responses (MMRs obtained from deviant-standard subtraction waves were not reported).

Importantly, longitudinal studies have shown that the presence or absence of certain auditory brain responses in early infancy is associated with future reading fluency (Van Zuijen et al., 2013; Schaadt et al., 2015). For example, later non-fluent readers were shown to have absent MMRs to consonant changes in a syllable in early infancy (Van Zuijen et al., 2013; Schaadt et al., 2015). However, no association between the absence of MMR to frequency changes in infants at risk of dyslexia and their later reading skills has been found by Leppänen et al. (2010). Possibly, neural speech-sound discrimination is more strongly associated with dyslexia than non-speech-sound processing, in line with the phonological processing deficit model. Since brain responses in infancy were found to be associated with later language development and reading skills in pre-school and school age (Molfese, 2000; Guttorm et al., 2005; Leppänen et al., 2010, 2012; Schaadt et al., 2015; Lohvansuu et al., 2018) and even earlier (Benasich et al., 2006; Cantiani et al., 2016), it is vital to determine how they deviate in those at dyslexia risk from the typical pattern. Besides group differences in MMR amplitudes, atypical hemispheric lateralization of the MMR was found in dyslexia-risk infants (Pihko et al., 1999; Guttorm et al., 2001; van Leeuwen et al., 2008; Leppänen et al., 2010). Notably, the results on lateralization of brain responses to sound and speech-sound changes, repeatedly found to be atypical in at-risk than control group, are not consistent throughout the previous studies. Some studies might be compromised by small, uneven, and/or unmatched sample sizes, and different stimuli and change types in different studies might have resulted in variable results (as, e.g., in Leppänen et al., 1999; Van Zuijen et al., 2013). Small sample sizes are particularly problematic in infant studies, as infant ERPs exhibit a large variance within and across individuals. Furthermore, as only a part of infants at familial risk of dyslexia will develop the disorder (Fisher and DeFries, 2002) and as only a subgroup of them demonstrates extensive auditory

processing deficits (Hämäläinen et al., 2013), large sample sizes are essential to detect signs of auditory dysfunctions.

1.3. Aims and hypotheses of the current study

We aimed to investigate the nature of impaired speech-sound discrimination in a large sample of newborn infants at high familial risk of dyslexia based on a parental diagnosis of moderate to severe dyslexia, using a more extensive stimulus set than previous studies. We recorded ERPs to pseudowords and MMRs to vowel duration, sound frequency of syllables, and vowel identity changes embedded in pseudowords. This is the first part of a longitudinal study (the DyslexiaBaby study, see Virtala and Partanen, 2018) in which the effects of parental dyslexia risk, and of an early passive music intervention on neural speech-sound processing and language development, will be investigated in infants from birth to pre-school or school age. The duration, frequency, and vowel deviances were chosen since the accurate detection of these features is essential in order to perceive speech sounds and word boundaries. First, we hypothesized that the ERP to the pseudoword could be diminished in at-risk infants. Second, we expected to find absent or diminished MMRs in these infants. Third, with an additional control paradigm, in which the long duration deviant was repeated alone (Schröger and Wolff, 1998), we tested whether the MMRs obtained to duration changes reflect genuine duration change detection or whether the acoustic stimulus duration differences affect the MMRs (Kushnerenko et al., 2001). Fourth, based on previous studies, both the MMRs and the ERPs to standard stimuli were expected to exhibit an atypical lateralization in high-risk infants.

2. Methods

2.1. Participants

The recruitment and participant selection process for this study is illustrated in Fig. 1. Families were recruited via traditional and social media, maternity clinics and wards, and via the website of the DyslexiaBaby study. The recruitment focused mainly on parents with dyslexia, but also control families were recruited with the same strategies. Two hundred and eight healthy full-term (gestational age at least 37 weeks, age at measurement 0.5–17 days, birth weight at least 2500 g) Finnish newborns with normal hearing, having passed the routine screening in the hospital (Evoked Oto-Acoustic Emissions, EOAE), participated in the longitudinal study.

In order to be included in the at-risk group, one or both of the infant's biological parents had to have developmental dyslexia, confirmed by a recent diagnostic statement from a health care professional or dyslexia testing in the present study, in addition to a report of reading- and writing-related difficulties in childhood. Dyslexia testing consisted of questionnaires, interviews, and a Finnish standardized test measuring oral text, word, and pseudoword reading, as well as writing speed (Nevala et al., 2006). For the at-risk group, exclusion reasons were an individualized curriculum in elementary school of the dyslexic parent (potentially indicative of broader cognitive deficits), brain trauma of the dyslexic parent in childhood (possible non-heritable cause of dyslexic symptoms of the parent), and suspected or confirmed attention deficits in one or both parents (comorbid with dyslexia and may affect auditory ERPs, see, e.g., Yang et al., 2015). The present study reports a sub-sample of high-risk infants, selected according to test results of the parents, in which for at least one parent moderate to severe dyslexia had to be confirmed by a below-norm performance of at least 2 standard deviations (*SD*) in reading or writing speed or accuracy in two or more of the subtests.

In order to be included in the control group, both of the infant's biological parents (or one on the behalf of both parents if the other parent was not available) had to report neither suspected nor diagnosed dyslexia nor other language- or learning-related disorders. Infants, whose epoched electroencephalography (EEG) data resulted in less than 50 accepted epochs for at least two deviant types were excluded (Fig. 1).

The final sample included 44 newborns at high risk of dyslexia (high-risk group), and 44 at no risk of dyslexia (control group; Table 1, Fig. 1). The groups did not differ in gender, gestational and measurement age, mothers' and fathers' educational background, or birth height and weight at a significance level of 5% (Table 1).

The Ethics Committee for Gynaecology and Obstetrics, Pediatrics and Psychiatry of the Hospital District of Helsinki and Uusimaa approved the study protocol and the study was performed in compliance with the Declaration of Helsinki. One or both parents of the newborn participants gave written informed consent to participate in the study prior to the experiment.

2.2. Stimuli and recordings

A bi-syllabic Finnish pseudoword /tata/ and its variants were used as auditory stimuli (first used by Pakarinen et al., 2014). It was uttered by a female native Finnish speaker, with the stress on the first syllable and a natural ending. The total duration of the stimulus was 300 ms, of which ≈251 ms were audible. The second syllable onset was at ≈168 ms, and the onset of the second /a/ at ≈181 ms (Fig. 2b).

In the auditory variants (Table 2), the change occurred in the second syllable, in syllable frequency (/ta-^{ta}/), vowel duration (/ta-ta:/), or vowel identity (/ta-to/). Variants were constructed by editing the /tata/ sound file (Adobe Audition CS6, 5.0, Build 708 and Praat 5.4.01). In all variants, the sound intensity level was root-mean-square (RMS) normalized to match the average intensity level of the /tata/ stimulus. Human (e.g., sigh, cry, laugh) and non-human (e.g., telephone ring, electric drill) novel sounds (duration 200 ms) were presented very rarely among the standard and deviant stimuli. Responses recorded to these stimuli will be reported elsewhere.

The sounds were presented in a mixed multi-feature-oddball paradigm (Fig. 2a) in at least four ≈7-min-long stimulus blocks. More data were recorded when the infant stayed calm. The pseudoword /tata/ was presented as the standard stimulus (probability on average 70.1%), its variants with a duration, frequency, or vowel identity change were occasionally presented as rare deviants (on average 25.3%, each individual deviant ≈8.5%), and the novel sounds were presented very rarely (on average 4.5%). One block contained 472 stimuli in total. Each deviant was presented at least 160 times and not more than 320 times during the experiment. The stimuli were presented with a varying stimulus-onset asynchrony (SOA) of 900 ± 50 ms (randomly alternating between 850, 860, 870, . . ., 940, 950 ms) in order to reduce expectancy effects related to the predictability of the stimulus onset, and to minimize an accumulation of non-phase-locked external periodic signals, such as line noise, in the ERP average. The order of the stimuli was pseudo-randomized so that two deviants and novels were never presented in a row (i.e., a deviant or novel sound was always followed by a standard). The blocks started with four standard stimuli in a row. An additional block containing a control paradigm with 200 repetitions of the vowel duration deviant only (≈3 min with the same varying SOA) was presented last, i.e., after four blocks, to obtain a controlled deviant-minus-standard difference for the duration

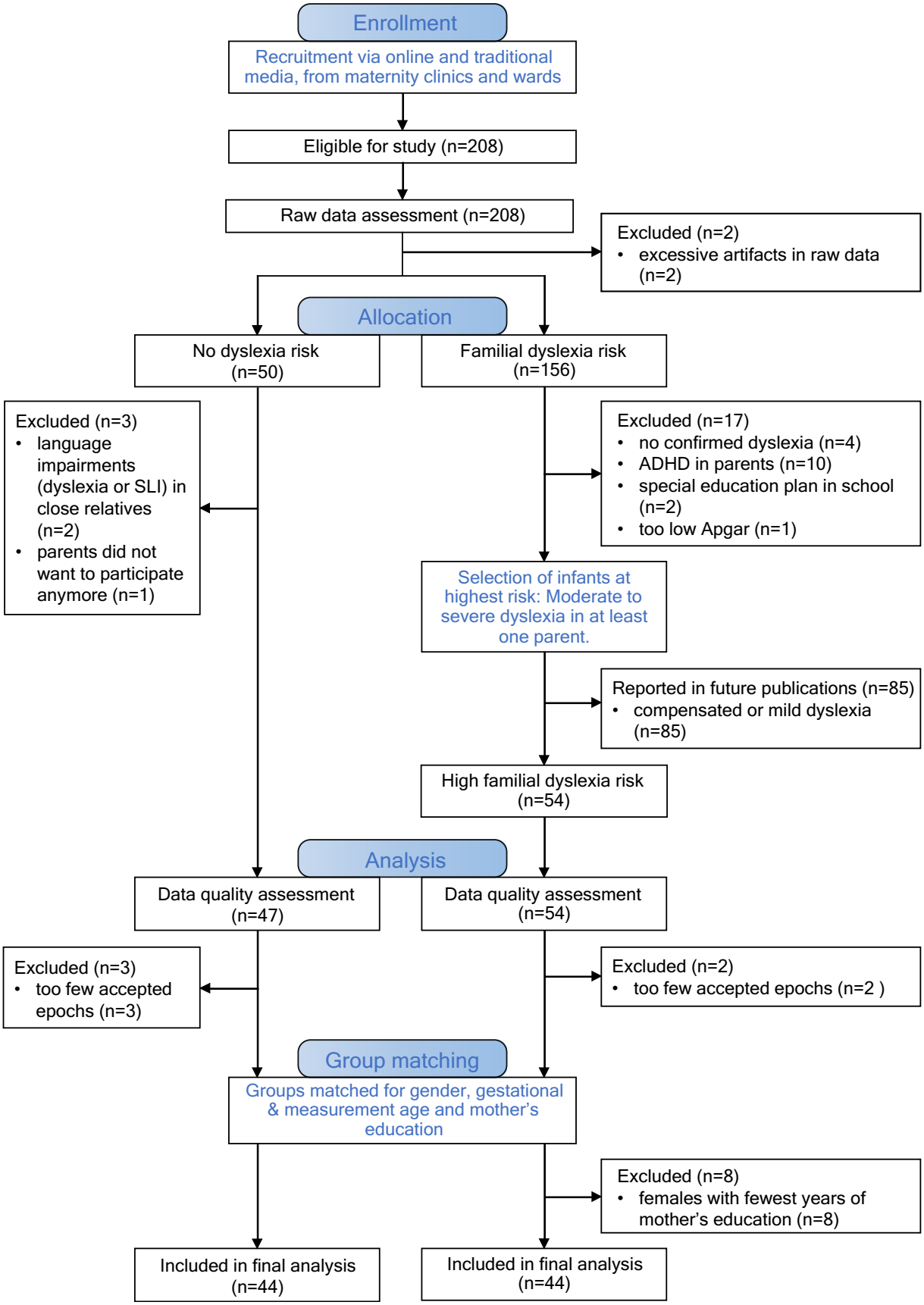

Fig. 1. Flow chart illustrating participant recruitment and allocation to groups.

Table 1
Background data (mean, *M*, in bold, and standard deviation, *SD*) of newborn participants and independent-sample *t*-statistics including degrees of freedom (*df*) and statistical significance (*p*) for group differences.

Variable	Control group		High-risk group		*T*-statistics		
	M	*SD*	***M***	*SD*	*t*	*df*	*p*
N (male/female)	44 (25/19)		44 (25/19)				
Gestational age [weeks]	**40.1**	1.1	**40.1**	0.9	0.15	86	.885
Age at measurement [days]	**8.9**	5.1	**9.1**	4.0	−0.26	86	.798
Mother's education [years]	**17.6**	2.6	**17.0**	2.2	1.06	83	.293
Father's education [years]	**16.8**	3.1	**15.5**	3.2	1.83	80	.070
Birth weight [g]	**3558**	545	**3608**	386	−0.50	86	.616
Birth height [cm]	**50.9**	2.2	**50.9**	1.9	0.05	86	.959
5-min Apgar score (range)[a]	**8–10**		**8–10**				

[a] Two high-risk infants had missing Apgar values, but were considered healthy, as there were no reported complications at birth. One high-risk infant had missing EOAE values due to a broken measurement machine, but the consequent hearing test in the maternity clinic indicated normal hearing. Therefore, these three infants were included in the final sample.

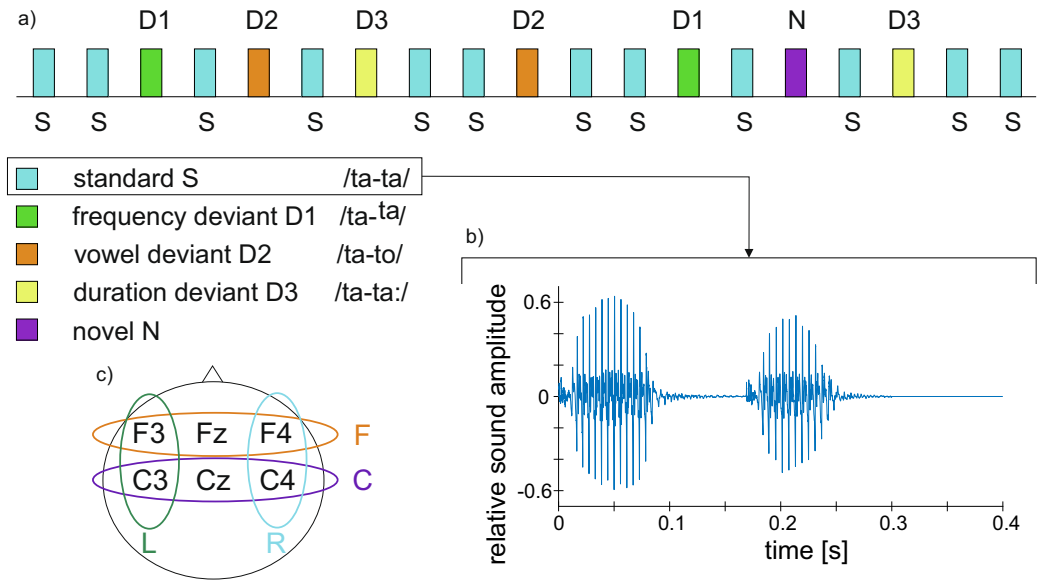

Fig. 2. Experimental setup. (a) The stimulus paradigm used. The Finnish pseudoword /tata/ was presented as a frequent standard (S, blue) and its auditory deviations (frequency, vowel and duration deviants D1–D3, green, orange, yellow, respectively) as rare deviant stimuli. Novel auditory stimuli were presented very rarely. (b) Waveform of /tata/ pseudoword. The sound amplitude is shown on a relative scale with the theoretical maximum of 1. (c) Formation of channel regions of interest (ROIs) from single EEG electrodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Description of auditory variants.

Deviant	Notation	Description of change
Duration	/ta-ta:/	Length of second syllable increased from 71 ms to 158 ms by copy and paste of the /a/-phoneme; total length 400 ms, of which approximately 327 ms were audible
Frequency	/ta-^{ta}/	Increase of fundamental frequency (F0) level of second syllable from 175 Hz to 225 Hz (5 semitones higher)
Vowel change	/ta-to/	Replacement of second /ta/ syllable with /to/ syllable as part of naturally uttered pseudoword /ta-to/ (Pakarinen et al., 2014); start time and duration of second syllable matched to /tata/ stimulus; F0-controlled to match F0-level of /tata/ stimulus

deviant. The total experiment duration was approximately one hour.

EEG recordings (sampling rate: 500 Hz, low-pass filter: 100 Hz, high-pass filter: 0 Hz) were carried out at Jorvi Hospital of Helsinki University Hospital in Espoo, and at a laboratory of the University of Jyväskylä, both in Finland. EEG was recorded with 18 active electrodes (headcap: ActiCap; amplifier: BrainProducts QuickAmp 10.08.14; software: BrainVision Recorder 1.20.0801; all: Brain Products GmbH, Gilching, Germany) placed according to the international 10/20 system (Fp1/2, F7/8, F3/4, Fz, C3/4, Cz, P7/8, P3/4, Pz, Oz, LM, RM). The data were referenced online to the average of all electrodes.

During the recording, the newborns were lying on their back in a crib and the auditory stimuli were presented with Presentation 17.2 Software (Neurobehavioural Systems Ltd., Berkeley, CA, USA) via a Genelec speaker placed approximately 40 cm from the newborn's head. The stimulus intensity was ≈65 dB at the infant's head (sound pressure level, SPL), the background noise of the room being ≈40 dB (SPL). The recording was conducted by a trained nurse or research assistant in a quiet hospital room (at Jorvi Hospi-

tal) or sound-proof laboratory (at University of Jyväskylä) who also determined the state of the infant with button presses on a response box (Cedrus RB844, Cedrus Corporation, California, USA) as 'active sleep', 'quiet sleep', 'awake', or 'intermediate sleep stage'. This classification was based on the guidelines of Grigg-Damberger (Grigg-Damberger et al., 2007). Infants of both groups spent equal relative amounts of time in active sleep (41% in control, 40% in high-risk group), quiet sleep (16% in control, 21% in high-risk group) and awake (19% in control, 15% in high-risk group) states.

2.3. Data analysis

The EEG data were pre-processed with MATLAB Release 2015a and 2017a (The MathWorks, Inc., Natick, Massachusetts, USA) as well as MATLAB toolboxes EEGlab 13.5.4b (Delorme and Makeig, 2004) and CBRUPlugin2.0b (Tommi Makkonen, Cognitive Brain Research Unit, University of Helsinki). First, data were inspected visually, and channels with continuous noise (e.g., due to poor scalp contact) were excluded from further analysis. Then, the data were filtered offline using a Hamming-windowed sinc finite impulse response filter between 0.5 (high-pass, 0.25 Hz cutoff frequency) and 25 Hz (low-pass, 28.125 Hz cutoff frequency). Thereafter, stimulus blocks with visually identified excessive movement artifacts were excluded from the analysis, and data of other blocks, except for the duration control block, were combined. Finally, the data were segmented into −100 to 840 ms epochs around stimulus onset separately for each stimulus, channel, and participant. The epochs of those standard stimuli that were immediately following a deviant were excluded from the analysis. Baseline correction was applied −100 to 0 ms prior to stimulus onset. The epochs with an amplitude exceeding ±120 μV in electrodes close to the eyes (Fp1, Fp2) were excluded to reduce eye-movement related artefacts. For all electrodes, epochs with amplitudes exceeding ±3 *SD* from the mean of the individual participant's average for each stimulus type and epochs with a drift of more than 80 μV from the start to the end of the epoch were rejected. The mean number of accepted epochs did not differ between groups (Table 3). As the final step of pre-processing, the data were re-referenced to the average of four electrodes: both mastoids (LM, RM) and electrode locations close to the mastoids (P7, P8) in order to display largest response amplitudes on fronto-central electrodes and to reduce the effects of often poor data quality on the mastoid electrodes. In 22 recordings, mastoids (20 cases, 8 in control, 12 in high-risk group) or P7/P8 (2 cases, 1 in control, 1 in high-risk group) had a poor signal, so that only mastoids or only P7 and P8 were used as references.

Six fronto-central electrodes were divided into four channel regions of interest (ROI): frontal, central, left, and right (Fig. 2c). In each ROI, the epoched data from the channels were averaged together in order to improve the signal-to-noise ratio, separately for each infant and stimulus type. Difference waves were obtained for all participants and each deviant by subtracting the standard-stimulus waveform from the deviant-stimulus waveform. Baselines were re-applied to −100 to 0 ms prior to change onset instead of stimulus onset and therefore differed between the deviants: for duration deviant 125–225 ms (change onset at 225 ms), and for frequency and vowel identity deviants 80–180 ms (change onset at 180 ms). For the duration change, an additional 'controlled' duration difference wave was calculated by subtracting the ERP elicited in the duration control block from the duration change waveform obtained in other recording blocks.

Amplitudes of ERP components to the standard stimulus and MMR amplitudes to the three deviant types were analyzed. The latencies of interest were determined by visual inspection of grand average ERPs to standard stimuli and deviant-minus-standard subtraction waveforms to each deviant type. Maximal peaks of grand average ERPs for standard stimuli and difference waves for deviant types were identified and a 100-ms (for broad reponses) or 50-ms (for narrow responses) time window (TW) was chosen centered at this peak latency. For ERPs/MMRs with several peaks, the corresponding amount of TWs was selected, so that they covered ERPs/MMRs of both groups. This resulted in two TWs (TW 1, TW 2) to the standard stimulus, in three TWs (TW I, TW II, TW III) to duration and frequency changes, and in four TWs (TW I, TW II, TW III, TW IV) to vowel identity changes. The MMR to the duration control stimulus was calculated from one TW (TW III). TW I (referred to as early MMR responses from now on) represents activity that has its peak between 200 and 500 ms from stimulus onset. TW II represents activity that has its peak between 500 and 700 ms, TW III between 700 and 800 ms, and TW IV later than 800 ms, all from stimulus onset (referred to as late MMR responses from now on).

To test whether the ERPs and MMRs were statistically significant at an alpha level of 0.05, the mean ERP/MMR amplitudes in the chosen TWs were compared to zero using one-sample *t*-tests at the ROI with the maximal response amplitude (one test per TW at the maximum ROI, equals 13 one-sample *t*-tests). Effect sizes are reported as Cohen's *d*. The statistical analyses were carried out with SPSS 24 (IBM, Armonk, New York, US).

Repeated-measures ANOVAs (2 × 2) were separately run for the responses elicited by the standard stimulus and each deviant type (duration, duration control, frequency, vowel identity) and each TW (1, 2, I, II, III, IV) with frontality (F, C) as within-subjects factor and group (control, high-risk) as between-subjects factor (one ANOVA per TW, equals 12 ANOVAs, as TW1 of ERPs to standard responses was not significant in any group). Amplitude differences between the groups were assessed only if the ERP/MMR amplitude differed statistically significantly from zero (hereafter: was significant) in at least one group.

Front-back distributions and their interactions with group were assessed only if the ERP/MMR was significant in both groups using similar ANOVAs as above (one ANOVA per TW for responses significant in both groups, equals 5 ANOVAs). Hemispheric differences and laterality × group interactions were investigated applying the same criteria with separate ANOVAs with laterality (L, R) as within-subjects and group (control, high-risk) as between-subjects factor (one ANOVA per TW for responses significant in both groups, equals 5 ANOVAs).

Table 3
Means (*M*, in bold) and standard deviations (*SD*) of accepted epochs for standard and deviant stimuli in control and high-risk groups and independent-samples *t*-statistics including degrees of freedom (*df*) and significance levels (*p*) for differences of accepted epochs between groups.

Deviant	Control group		High-risk group		*T*-statistics		
	M	*SD*	***M***	*SD*	*t*	*df*	*p*
Standard	**487**	153	**529**	140	−1.32	86	.188
Duration	**102**	33	**110**	30	−1.20	86	.232
Frequency	**103**	32	**111**	31	−1.15	86	.253
Vowel identity	**104**	34	**112**	30	−1.08	86	.282
Duration control	**131**	27	**136**	27	−0.80	84	.426

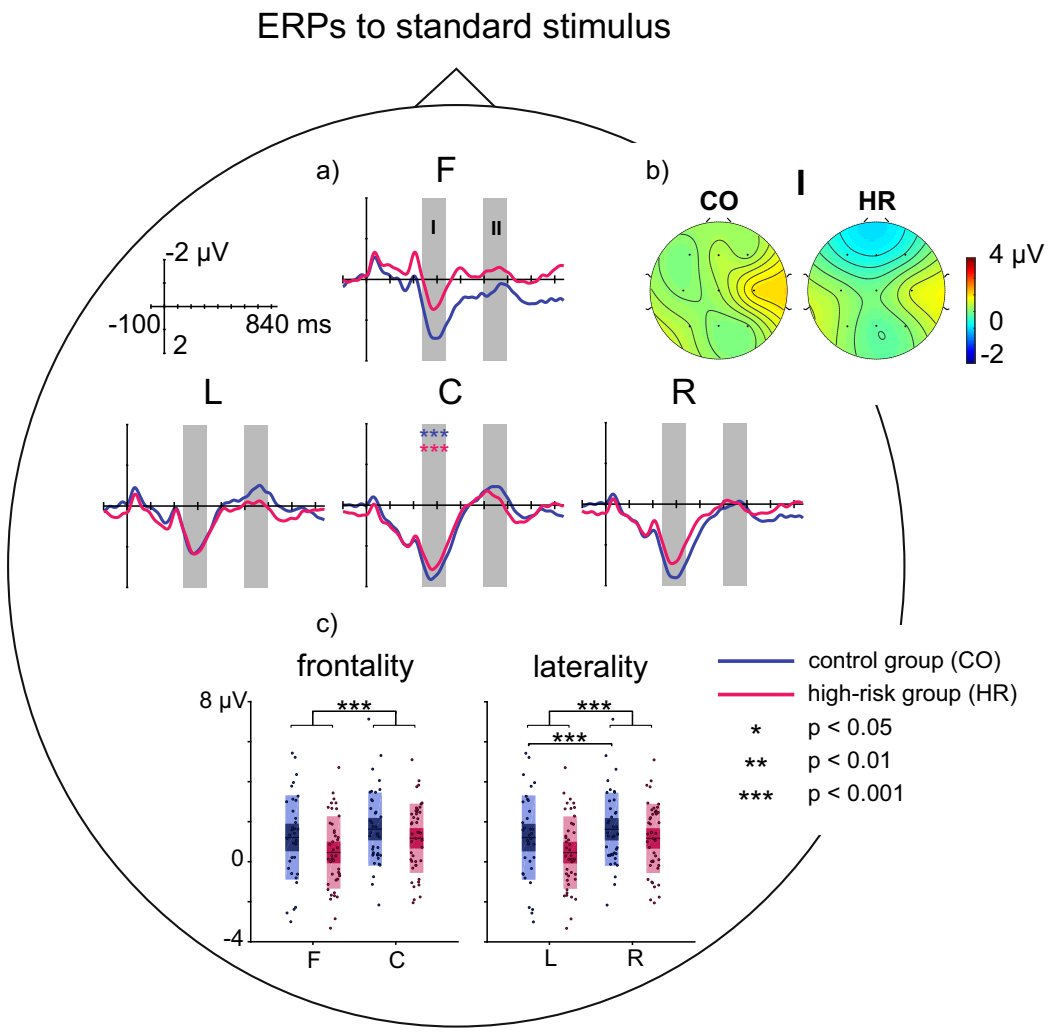

Fig. 3. ERPs to standard stimulus /tata/ from the control group (CO, blue) and high-risk group (HR, pink). (a) Grand average ERPs in control and high-risk group at channel regions of interest F (frontal), C (central), L (left), and R (right). Colored asterisks indicate the level of significance of the standard response in the selected time window for the ROI with maximal amplitude for the respective group as verified by one-sample t-tests. (b) Distribution of standard ERPs on the scalp for the early positivity (I). (c) Frontality, laterality and group effects. Each individual data point reflects the average mean amplitude of one participant, dark horizontal bars are group means, dark shaded areas mark standard errors of group means, and light shaded areas mark standard deviations. Asterisks indicate the level of significance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
ERP amplitudes of both groups (control group, high-risk group) to the standard stimulus. listed are means (in bold) in µV and standard deviations (in parentheses) in µV at the channel region of interest (C – central channels) with the maximal amplitude in selected time windows (TW; 1, 2), and one-sample *t*-statistics (*t*, *df* – degrees of freedom, in parentheses, *p* – significance level, Cohen's *d* – effect size). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

ERP	Control group	High-risk group
TW 1 (233–333 ms)	*****1.62** (1.83) on C $t(40) = 5.70$, $p < .000$, $d = 0.89$	*****1.17** (1.73) on C $t(43) = 4.49$, $p < .000$, $d = 0.68$
TW 2 (497–597 ms)	−**0.39** (1.57) on C $t(40) = -1.60$, $p = .117$, $d = -0.25$	−**0.40** (1.46) on C $t(43) = -1.81$, $p = .077$, $d = -0.27$

Applicable corrections (Huynh-Feldt) were used when sphericity was violated (original degrees of freedom and corrected *F*- and *p*-values are reported). In post-hoc comparisons, Bonferroni correction was applied, and only corrected *p*-values are reported. Effect sizes are reported as partial eta squared (η_p^2).

3. Results

3.1. ERPs to standard /tata/

The pseudoword /tata/ evoked similar ERPs in both groups (Fig. 3a, scalp distribution in Fig. 3b). Visual inspection of the waveform suggested that the pseudoword elicited two narrow early negative deflections that are most likely onset responses to the two syllables of the pseudoword, followed by a broad positivity-negativity complex (Fig. 3a). The early positive component (233–333 ms, TW 1) was statistically significant (hereafter: significant) in both groups (Table 4) and did not significantly differ between groups in amplitude ($p = .128$). ANOVA results (Table 5, Fig. 3c) revealed that the response was significantly larger at central compared to frontal channels (TW 1, frontality main effect, $p < .001$), and significantly larger at the right than left hemisphere (TW 1, laterality main effect, $p < .001$). A significant laterality × group interaction effect was found ($p = .008$), and post-hoc

Table 5
Results of the repeated-measures ANOVAs. Shown are *F*-values with degrees of freedom (*df*1, *df*2), statistical significance (*p*) and effect sizes (η_p^2) of significant and trending group (control, CO vs. high-risk, HR), frontality (frontal vs. central), laterality (left vs. right), and interaction effects for all ERP components to the standard stimulus (STD) and MMRs to speech-sound deviants (DUR - duration, DURC - controlled duration, FRE - frequency, VOW - vowel, in all time windows, TW, polarity, pol., indicated as positive, +, or negative, −) and their significant or trending post-hoc comparisons (mean difference, *MD*, and standard error of mean, *SEM*, and statistical significance, *p*). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

Component	ANOVA				Post-hoc comparisons			
TW (pol.)	Effect	*F(df1, df2)*	*p*	η_p^2	Comparison	*MD (SEM)* [μV]	*p*	Result
ERPs to STD								
1 (+)	Group	2.37(1, 74)	.128	.03				
	Frontality	23.79(1, 74)	***<.001	.24	Frontal vs. central	−0.699 (0.143)	***<.001	Frontal < central
	Laterality	19.19(1, 65)	***<.001	.23	Left vs. right	−0.505 (0.115)	***<.001	Left < right
	Laterality × group	7.56(1, 65)	**.008	.10	Left vs. right in CO	−0.823 (0.171)	***<.001	Left < right in CO
2 (−)	ERP not significant in any group, no further statistical analysis							
MMRs to DUR								
I (−)	Group	4.54(1, 74)	*.036	.06	HR vs. CO	0.750 (0.352)	*.036	HR < CO
II (+)	Frontality	4.68(1, 74)	*.034	.06	Frontal vs. central	0.598 (0.276)	*.034	Frontal > central
III (+)	Laterality × group	3.89(1, 65)	.053	.06				
MMRs to DURC								
III (+)	No significant group, frontality, laterality, and interaction effects							
MMRs to FRE								
I (−)	Group	3.36(1, 74)	.071	.04				
II (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
III (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
MMRs to VOW								
I (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
II (+)	Group	3.18(1, 74)	.079	.04				
III (+)	Laterality × group	4.41(1, 65)	*.040	.06	HR vs. CO at right	−1.283 (0.662)	.057	
					Left vs. right in CO	−0.860 (0.358)	*.019	Left < right in CO
IV (+)	No significant group, frontality, laterality, and interaction effects							

tests indicated that the response was significantly larger at the right than left hemisphere in the control group only ($p < .001$). The late negative response (497–597 ms, TW 2) was not significant in either group (Table 4, cf. at central channels in high-risk group, $p = .077$), and thus, no further statistical analysis was pursued.

3.2. MMRs to duration, frequency, and vowel identity changes

MMRs to speech-sound changes in duration, frequency, and vowel identity are illustrated in Fig. 4a, MMRs to controlled duration changes in Fig. 5, and the results on tests comparing them to zero are listed in Table 6. Duration changes elicited a significant negative MMR in the control group at 290–340 ms after stimulus onset (TW I), but no such response in the high-risk group. In addition, these changes elicited a significant positive MMR at 502–602 ms (TW II) and 677–777 ms (TW III) in both groups. Duration changes in the controlled duration condition elicited a significant positive MMR at 641–741 ms (TW III) in both groups. Frequency changes elicited no significant negative MMR in the high-risk group, but in the control group a significant negative response was found at 252–302 ms (TW I). A significant positive MMR to frequency changes was elicited at 578–678 ms (TW II) and 740–840 ms (TW III) in the high-risk group only. Vowel changes elicited a broad positive MMR, which was significant in the high-risk group at 715–765 ms (TW III) and 790–840 ms (TW IV), and in the control group at TWs I–IV.

The ANOVA results on MMR group, frontality, laterality, and their interaction effects are visualized in Fig. 4c and summarized in Table 5. To duration changes, the negative MMR (TW I) was significantly smaller in high-risk than in control infants (group main effect, $p = .036$). The positive MMR to duration changes (TW II) was significantly larger at frontal than central channels across groups (TW II, frontality main effect, $p = .034$). For TW III, a laterality × group interaction did not reach significance ($p = .053$). In the controlled duration change condition, no significant group, frontality, laterality, or interaction effects were found. Although in Fig. 4 there seem to be amplitude differences to frequency (TW I) and vowel changes (TW II), results did not reach significance ($p = .071$ and .079, respectively). To vowel identity changes at TW III, a significant laterality × group interaction was found ($p = .040$), driven by significantly smaller MMRs in the left compared to right hemisphere in the control group only ($p = .019$).

4. Discussion

This study aimed at determining the nature of deficits in neural encoding and discrimination of speech sounds in newborn infants at familial risk of dyslexia. To this end, ERPs to a repeated Finnish pseudoword /tata/ and MMRs to three types of changes embedded in it were recorded from newborns at high familial risk or no familial risk of dyslexia, and the response amplitudes and scalp distributions were compared between the groups. An early positive ERP component to the pseudoword was elicited at 233–333 ms in both groups, the response amplitudes not differing between the groups. However, the MMRs to speech-sound changes differed between the groups in several ways: Firstly, at early latencies negative MMRs to duration (at 290–340 ms) and frequency changes (at 252–302 ms) were elicited in the control group, but were absent in the high-risk group. A group comparison at these early latencies indicated significantly smaller MMR amplitudes to duration changes. Secondly, the high-risk group had late positive MMRs (at 578–678 ms and 740–840 ms) to frequency changes, which were absent in the control group. Thirdly, late positive MMRs (at 715–765 ms) were lateralized to the right hemisphere for vowel changes in the control group. Taken together, these results suggest an extensive pattern of speech discrimination dysfunctions in newborns with a high familial risk of dyslexia.

4.1. ERPs to standard pseudowords

The repeating pseudoword elicited an early positive ERP response with a central- and right-preponderant scalp distribution in both groups. The standard ERP waveform consisted of two main

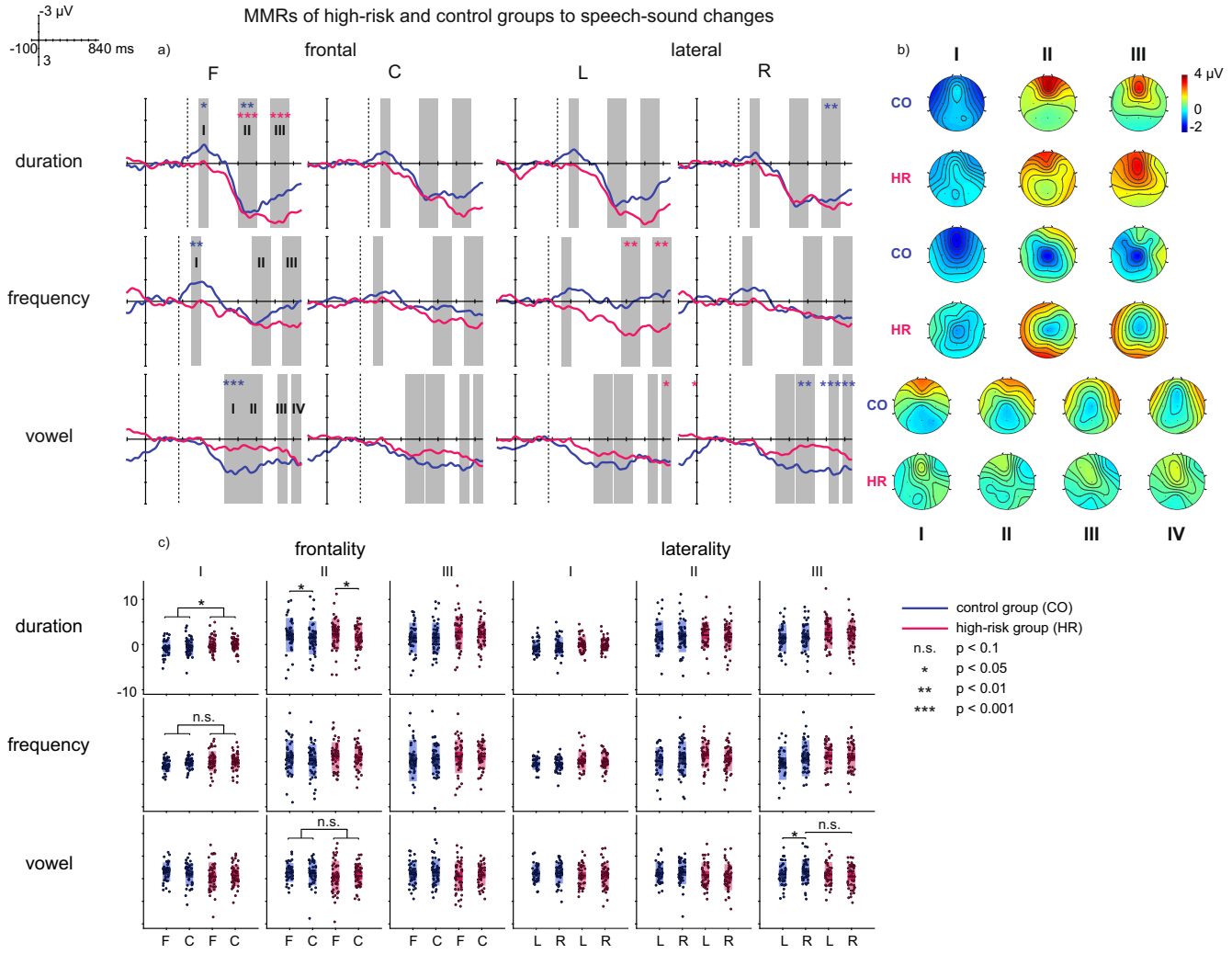

Fig. 4. MMRs at channel regions of interest F (frontal), C (central), L (left), and R (right) of the high-risk (pink) and control groups (blue) to duration, frequency, and vowel identity changes. (a) Difference curves. Change onset is marked by a vertical dotted bar preceded by a pre-stimulus baseline of 100 ms. Latency windows are marked with a gray bar and roman numerals (referred to in the text). Asterisks depict MMRs' significances on the ROI with maximal amplitude as evaluated by one-sample *t*-tests. Groups are differentiated by colours. (b) Distribution of MMRs on the scalp in the control group (CO) and high-risk (HR) group in all latency windows marked by roman numerals. (c) Frontality, laterality, and group effects. Each individual data point represents the mean MMR amplitude of one participant, dark horizontal bars are group means, dark shaded areas mark standard errors of group means, and light shaded areas mark standard deviations. Asterisks and n.s. indicate the level of statistical significance for group, hemispheric, or post-hoc comparisons of interaction effects (depicted by horizontal bars) resulting from ANOVA analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

components: an early positivity peaking at 283 ms and a wide late negativity peaking at 547 ms from stimulus onset, consistent with previous studies (Molfese, 2000; Guttorm et al., 2001; Wunderlich et al., 2006). While the early positivity was significant in both groups with relatively large effect sizes, the negative response was not significant in either group. No group differences were found for the amplitudes or hemispheric distribution of the early positivity, which suggests that familial risk of dyslexia might not influence this early level of basic speech-sound encoding.

The distribution of the early positive ERP component in the present study was maximal over the right hemisphere at central channels in both groups. Hemispheric lateralization of speech processing in infants has varied between studies, with some suggesting an enhanced left-hemispheric lateralization (Molfese et al., 1975; Dehaene-Lambertz, 2000), and others suggesting right-hemispheric processing (Perani et al., 2011). Also ERPs to tones with different harmonics were found to be larger over the left than right hemisphere (Dehaene-Lambertz, 2000), suggesting left-lateralized processing for non-speech sounds in infants. Our results with a right-hemispheric lateralization of the responses to the standard stimuli are in line with the functional magnetic resonance imaging (fMRI) study by Perani et al. (2011) in newborns. In our study, the large number of subjects (88 newborns) and the number of analyzed EEG epochs for standard stimuli were large rendering a good signal-to-noise ratio (mean of 508 artifact-free EEG epochs). Therefore, the results can be considered reliable. However, they should be confirmed with a method yielding better source-localization accuracy. To summarize, the ERPs to pseudowords suggest that the cortical encoding of repetitive speech sounds might not be influenced by familial dyslexia risk at birth and, further, that speech processing or auditory processing in general might be differently lateralized at birth than later in development.

4.2. Group differences in MMR amplitudes

In contrast with the non-existent group differences for the ERPs to the standard stimulus, the MMRs to speech-sound deviants differed between the groups in several ways. We found early negative MMRs to duration and frequency changes in control infants that

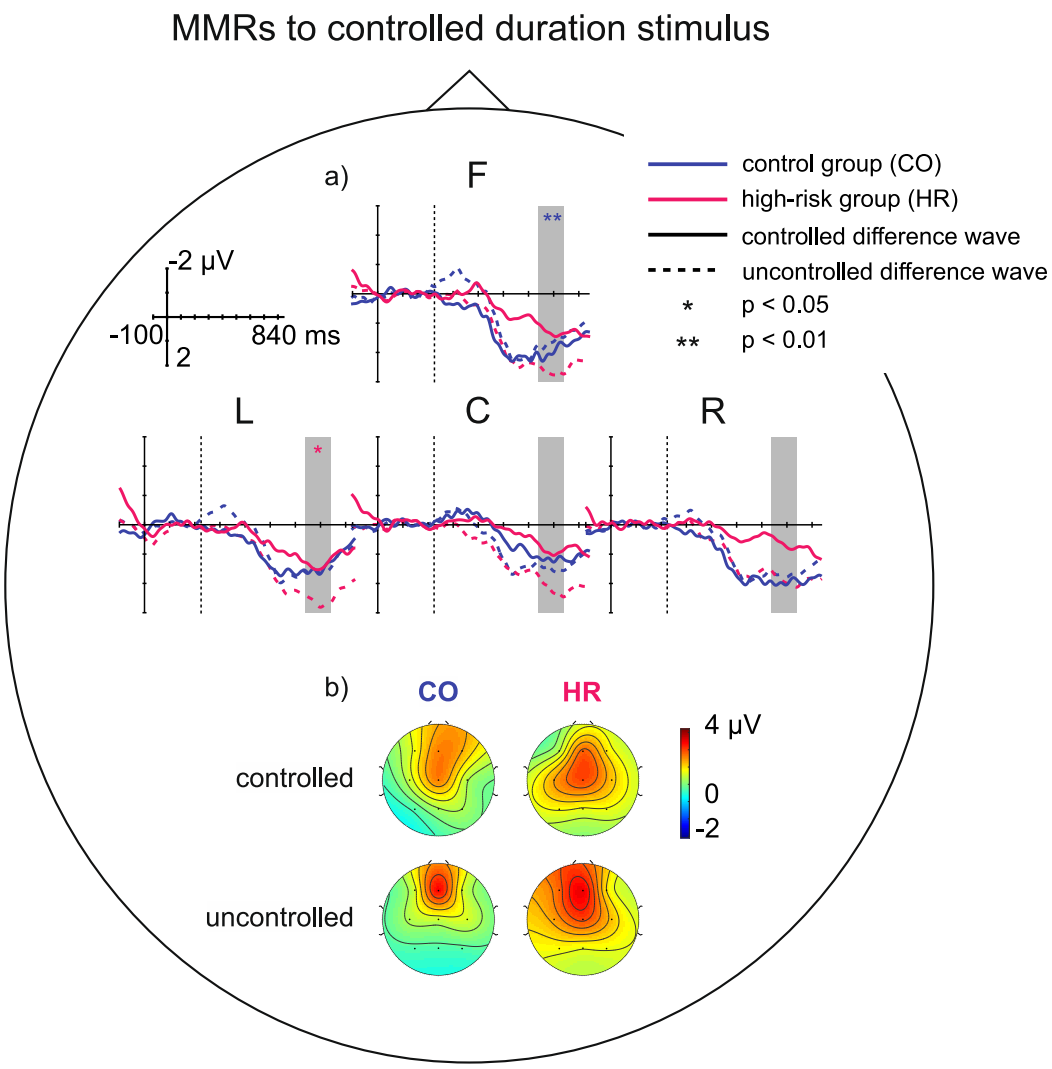

Fig. 5. (a) MMRs (difference waves) in the controlled duration condition (continuous line; duration deviant ERP was compared to the ERP to the same stimulus acting as a standard) compared to uncontrolled condition (dotted line). Change onset is marked by a vertical dotted bar preceded by a pre-stimulus baseline of 100 ms and the latency of interest is marked with a gray bar. Asterisks depict the controlled MMRs' significances as evaluated by one-sample *t*-tests. Groups are differentiated by colours. (b) Distribution of MMRs in controlled (641–741 ms) and uncontrolled (677–777 ms) conditions on the scalp for control group (CO) and high-risk (HR) group.

were absent in high-risk infants. Furthermore, the comparison of the early MMR amplitudes between the groups indicated significantly smaller amplitudes to duration changes in the high-risk than control group. Late positive MMRs to frequency changes were only present in the high-risk group and absent in the control group. Vowel changes, in turn, elicited late positive MMRs in both groups. Previous studies demonstrating deficient auditory processing in newborns at risk of language impairments used non-speech sounds (Leppänen et al., 2010), speech sounds with one deviant type only (consonant duration, Leppänen et al., 1999), or involved older infants (Leppänen et al., 2002; Benasich et al., 2006; van Leeuwen et al., 2008; Van Zuijen et al., 2013; Schaadt et al., 2015). In our study, absent or diminished MMRs were found to two out of three deviant types presented to infants at high risk of dyslexia, suggesting several neural change detection irregularities in high-risk infants already at birth.

In the present study, MMRs of both negative and positive polarity were elicited in newborns, consistent with some previous studies (Friederici et al., 2002; Háden et al., 2009; Virtala et al., 2013). Whereas duration, frequency, and vowel deviants demonstrated a positive MMR around 250–600 ms from stimulus onset in both groups (except for frequency change in the control group), it was preceded by a negative deflection at around 250–350 ms in response to the duration and frequency changes in the control group only. Co-existing negative and positive MMRs have been reported also previously in infants, as reviewed in the introduction. In the present study, the negative responses to the duration and frequency deviants peaked very early, at around 90 ms and 100 ms from deviance onset, respectively. Similar early-latency negative responses to auditory deviants have been reported in infants also previously (Kushnerenko et al., 2007; Háden et al., 2009).

The emergence of an early negative component in the difference waveform has been interpreted as a sign of neural maturation (Trainor et al., 2003). The co-existence of fast negative MMRs and slow positive MMRs in the present results could thereby reflect a maturational stage where the negative MMR starts to appear, while the positive MMR gradually disappears. Alternatively, the positive MMR was suggested to develop towards the adult P3a, reflecting maturation of the auditory attention network (Kushnerenko et al., 2013). While the maturational pathways of the negative and positive MMRs and their underlying functions are still under debate, both components are thought to reflect aspects of an auditory change detection mechanism in infancy,

Table 6
MMR amplitudes of both groups (control group, high-risk group) to the deviant types (DUR – duration, DURC – controlled duration, FRE – frequency, VOW – vowel). Listed are means (in bold) in μV and standard deviations (in parentheses) in μV at the channel region of interest (F – frontal, C – central, R – right, L – left channels) with the maximal amplitude in selected time windows (TW; I, II, III, IV), and one-sample *t*-statistics (*t*, *df* – degrees of freedom, in parentheses, *p* – significance level, Cohen's *d* – effect size). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

MMR	Control group	High-risk group
DUR TW I (290–340 ms)	*−**0.75** (1.82) on F $t(35) = -2.48$, $p = .018$, $d = -0.41$	−**0.06** (1.44) on R $t(42) = -0.28$, $p = .783$, $d = 0.04$
DUR TW II (502–602 ms)	****2.12** (3.77) on F $t(35) = 3.38$, $p = .002$, $d = 0.56$	*****2.34** (3.47) on F $t(42) = 4.42$, $p < .000$, $d = 0.67$
DUR TW III (677–777 ms)	****1.69** (3.08) on R $t(40) = 3.52$, $p = .001$, $d = 0.55$	*****2.65** (3.72) on F $t(42) = 4.68$, $p < .000$, $d = 0.71$
DURC TW III (641–741 ms)	****1.99** (3.64) on F $t(33) = 3.19$, $p = .003$, $d = 0.55$	***1.41** (3.38) on L $t(37) = 2.58$, $p = .014$, $d = 0.42$
FRE TW I (252–302 ms)	**−**0.85** (1.48) on F $t(35) = -3.45$, $p = .001$, $d = -0.57$	−**0.04** (1.88) on C $t(43) = -0.16$, $p = .877$, $d = -0.02$
FRE TW II (578–678 ms)	**0.86** (3.98) on F $t(35) = 1.30$, $p = .202$, $d = 0.22$	****1.47** (2.87) on L $t(37) = 3.17$, $p = .003$, $d = 0.51$
FRE TW III (740–840 ms)	**0.74** (3.99) on R $t(40) = 1.19$, $p = .241$, $d = 0.19$	****1.27** (2.79) on L $t(37) = 2.80$, $p = .008$, $d = 0.45$
VOW TW I (422–522 ms)	*****1.50** (2.09) on F $t(35) = 4.29$, $p < .000$, $d = 0.71$	**0.70** (2.37) on C $t(43) = 1.96$, $p = .057$, $d = 0.30$
VOW TW II (536–636 ms)	****1.43** (2.65) on R $t(40) = 3.44$, $p = .001$, $d = 0.54$	**0.79** (2.80) on L $t(37) = 1.75$, $p = .088$, $d = 0.28$
VOW TW III (715–765 ms)	*****1.56** (2.72) on R $t(40) = 3.68$, $p = .001$, $d = 0.57$	***0.96** (2.72) on L $t(37) = 2.18$, $p = .035$, $d = 0.35$
VOW TW IV (790–840 ms)	****1.32** (2.87) on R $t(40) = 2.94$, $p = .005$, $d = 0.46$	***1.14** (2.97) on L $t(37) = 2.37$, $p = .023$, $d = 0.38$

essential for and likely indicative of future sensory-cognitive development. The present results demonstrated negative MMRs in the control group only, whereas MMRs in high-risk infants had a positive polarity. In light of the above-reviewed literature, the missing negative MMRs in the high-risk group and the missing positive MMR in the control group to the frequency change could be interpreted as signs of less mature auditory neural development in the high-risk infants. As the negative MMR had an earlier latency than the positive MMR, neural auditory change detection in the control group can also be interpreted to be faster than in the high-risk group.

The absent early MMRs in the high-risk group to duration and frequency changes, and MMR amplitude differences between groups to duration changes suggest that the auditory system of the control group can distinguish more accurately between the different speech-sound changes than that of the high-risk group, in line with previous results showing diminished MMNs in dyslexic adults (Baldeweg et al., 1999; Kujala et al., 2003) and children (Maurer et al., 2003; Lovio et al., 2010). Also in young infants, similar evidence converges, as reviewed in the introduction.

The results of the aforementioned infant studies and our study demonstrate atypical speech-sound discrimination due to familial risk of dyslexia already in infancy. The ability to extract accurately speech-sound information and to discriminate speech sounds is important for typical language development involving the formation of neural representations of native language phonemes during the first year of life (Kuhl, 2004). Consequently, atypical speech-sound discrimination at birth could lead to a weak or slow formation of native language phoneme representations. This is supported by studies showing that poorer neural speech processing in infancy as demonstrated by auditory ERPs predicts compromised language skills in childhood (Molfese, 2000; Guttorm et al., 2005; Leppänen et al., 2010, 2012; Schaadt et al., 2015; Lohvansuu et al., 2018). Furthermore, the discrimination of, e.g., duration and frequency cues investigated in the present study is important for the detection of word boundaries (Friederici, 2005). They have to be detected to differentiate between single phonemes and to segment words during the filtering process of the incoming continuous speech stream (Jusczyk, 1999), which is relevant for language development. Problems in detecting word boundaries can therefore lead to further challenges in later language development. Several factors can influence the course of this future language development. With newborns, as examined in this study, it is possible to observe how speech stimuli are originally processed, prior to extensive influence from experience or environmental exposure. Each infant will then undergo maturational processes that depend largely both on genetic and environmental factors, which differ for each individual.

4.3. Effects of the controlled duration paradigm

The controlled duration paradigm was introduced to test whether the MMRs obtained reflect genuine duration discrimination instead of processing of the physical stimulus duration differences (Schröger and Wolff, 1998). As our duration deviant lasted 100 ms longer than the /tata/ standard, these physical differences in the offsets of the standard and deviant stimuli could result in a deflection in the difference waveform that reflected processing of merely physical differences between the stimuli. The early negative MMR that was observed in the uncontrolled duration condition in infants at no risk was not seen in the controlled condition. It may be that this early negativity was elicited due to the physical features of the stimulus change, i.e., longer stimulus duration resulting in a different obligatory ERP response (Jacobsen and Schröger, 2003). However, we found that a late positive MMR was still elicited in both groups when the stimulus differences were controlled for (i.e., when the duration deviant ERP was compared to the ERP to the same stimulus acting as a standard in the control condition). This supports and extends previous findings that the infant MMR reflects genuine change detection in the auditory system (Kushnerenko et al., 2002; Háden et al., 2016). Future studies should further investigate, what kind of sensory and cognitive functions these early negative and late positive MMRs reflect at birth.

4.4. MMR scalp distributions

We found significant interactions between laterality and group to vowel changes in the late positive MMR, which resulted from right-lateralized processing in the control group, whereas no such

effect was found in the high-risk group. This laterality finding of the present study is rather unexpected, since processing of speech in adults has repeatedly been suggested to be left-lateralized (Kimura, 1967; Tervaniemi and Hugdahl, 2003). Furthermore, in newborns and 2-month-old infants, left-lateralized MMRs were previously found in a healthy control group and right-lateralized MMRs in a group at risk of dyslexia to syllable duration changes (Pihko et al., 1999) and CVC syllable changes (van Leeuwen et al., 2008). Yet, some earlier findings on the lateralization of auditory change discrimination are consistent with ours. For example, control newborns and 2-month-old infants that turned into fluent readers had right-lateralized ERPs to deviant tone frequencies or MMRs to CVC syllable changes and at-risk newborns with later reading problems exhibited left-lateralized ERPs to deviant stimuli (Leppänen et al., 2010; Van Zuijen et al., 2013). The lateralization pattern in no-risk newborns in our study extends the dissenting literature on this topic in healthy infants. Future research should aim to clarify whether lateralization is influenced by, for instance, the use of non-speech vs. speech stimuli and the maturation of the auditory system.

The observed distinct MMR topography pattern in no-risk compared with high-risk infants in this study could stem from the cortical locations or orientations of MMR generators. However, this and most of previous infant EEG studies were not designed to estimate MMR sources. Due to a small amount of electrodes used in this study, the above-discussed findings on scalp distributions should be confirmed by studies designed for better source localization, e.g., using additional anatomical MRIs and high-density EEG or magnetoencephalography.

4.5. Summary and conclusions

Our novel results shed light on the nature of speech-processing deficits in newborns at high risk of dyslexia, showing an extensive pattern of atypical speech-sound discrimination in high-risk newborns including absent or weaker MMRs, as well as deviating MMR polarities compared to control newborns. These results, with larger group sizes and a more extensive stimulus set than in previous studies, support and extend previous findings. Irregularities in the neural discrimination of speech at newborn age could result in weak, inaccurate, or slow formation of neural speech-sound representations in the brain, which can be a precursor for impaired language and reading-skill acquisition. The findings of this study can contribute to unravel the early origins of dyslexia. Revealing the neural basis and nature of these speech processing deficits already at birth can assist in the design of targeted interventions to support language development from the beginning of life.

Conflict of interest

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

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