



Research report

A longitudinal study investigating neural processing of speech envelope modulation rates in children with (a family risk for) dyslexia



Astrid De Vos^{a,b,*}, Sophie Vanvooren^{a,b}, Jolijn Vanderauwera^{a,b},
Pol Ghesquière^b and Jan Wouters^a

^a Research Group Experimental ORL, Department of Neurosciences, KU Leuven – University of Leuven, Leuven, Belgium

^b Parenting and Special Education Research Unit, Faculty of Psychology and Educational Sciences, KU Leuven – University of Leuven, Leuven, Belgium

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ABSTRACT

Recent evidence suggests that a fundamental deficit in the synchronization of neural oscillations to temporal information in speech may underlie phonological processing problems in dyslexia. Since previous studies were performed cross-sectionally in school-aged children or adults, developmental aspects of neural auditory processing in relation to reading acquisition and dyslexia remain to be investigated. The present longitudinal study followed 68 children during development from pre-reader (5 years old) to beginning reader (7 years old) and more advanced reader (9 years old). Thirty-six children had a family risk for dyslexia and 14 children eventually developed dyslexia. EEG recordings of auditory steady-state responses to 4 and 20 Hz modulations, corresponding to syllable and phoneme rates, were collected at each point in time. Our results demonstrate an increase in neural synchronization to phoneme-rate modulations around the onset of reading acquisition. This effect was negatively correlated with later reading and phonological skills, indicating that children who exhibit the largest increase in neural synchronization to phoneme rates, develop the poorest reading and phonological skills. Accordingly, neural synchronization to phoneme-rate modulations was found to be significantly higher in beginning and more advanced readers with dyslexia. We found no developmental effects regarding neural synchronization to syllable rates, nor any effects of a family risk for dyslexia. Altogether, our findings suggest that the onset of reading instruction coincides with an increase in neural responsiveness to phoneme-rate modulations, and that the extent of this increase is related to (the outcome of) reading development. Hereby, dyslexic children persistently demonstrate atypically high neural synchronization to phoneme rates from the beginning of reading acquisition onwards.

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* Corresponding author. Research Group Experimental ORL, Department of Neurosciences, KU Leuven – University of Leuven, Herestraat 49 Box 721, B-3000 Leuven, Belgium.

E-mail address: astrid.devos@kuleuven.be (A. De Vos).

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1. Introduction

Developmental dyslexia is described as a learning disability, characterized by severe and persistent difficulties in reading and spelling despite normal intelligence, education, and intense remedial effort (Vellutino, Fletcher, Snowling, & Scanlon, 2004). Numerous behavioral studies have demonstrated that individuals with dyslexia show deficits in the phonological processing of speech (Ziegler & Goswami, 2005). However, the neural dysfunction underlying these phonological processing problems remains unknown.

Neural processing of the phonological structure of speech, represented by distinct temporal modulations in the speech envelope, is known to be mediated by synchronized activity of neural oscillations in the auditory cortex (Giraud & Poeppel, 2012; Peelle & Davis, 2012; Saoud et al., 2012). More specifically, synchronization of delta (<4 Hz) and theta (4–8 Hz) oscillations has been associated with the neural processing of syllable-rate information, as the frequency ranges of these slow oscillatory bands match the temporal rate at which syllables occur in speech (~4 Hz; Ding & Simon, 2014; Doelling, Arnal, Ghitza, & Poeppel, 2014; Peelle, Gross, & Davis, 2013). Similarly, synchronization of beta (13–30 Hz) and gamma (>30 Hz) oscillations has been associated with the neural processing of phoneme-rate information, as the frequency ranges of these fast oscillatory bands match the temporal rate at which phonemes occur in speech (~20 Hz; Luo & Poeppel, 2012; Morillon, Liégeois-Chauvel, Arnal, Bénar, & Giraud, 2012; Shamir, Ghitza, Epstein, & Kopell, 2009). On this basis, Goswami (2011) proposed a comprehensive framework, explicating that phonological processing problems in dyslexia might originate from (1) impaired neural synchronization of delta and theta oscillations, which causes a reduced sensitivity to syllable-rate information, resulting in deficient syllable-level representations and (2) the co-occurrence of impaired delta and theta synchronization with unimpaired gamma synchronization, which causes an increased sensitivity to phoneme-rate information, resulting in too specific phoneme-level representations.

Based on the framework of Goswami (2011), a number of studies have investigated oscillatory synchronization during auditory temporal processing in various dyslexic age groups, including school-aged children, adolescents, and adults. Studies investigating delta and theta synchronization in relation to syllable-rate processing have generally demonstrated synchronization deficiencies, although, there is stronger evidence for deviances in delta synchronization (Cutini, Szűcs, Mead, Huss, & Goswami, 2016; Hämäläinen, Rupp, Soltész, Szűcs, & Goswami, 2012; Molinaro, Lizarazu, Lallier, Bourguignon, & Carreiras, 2016; Power, Colling, Mead, Barnes, & Goswami, 2016; Soltész, Szűcs, Leong, White, & Goswami, 2013), than for an impairment in theta synchronization (Lizarazu et al., 2015). Results from studies investigating gamma synchronization in relation to phoneme-rate processing, are less conclusive. Neural synchronization of low-gamma oscillations (≤ 40 Hz) is found to be unimpaired (Cutini et al., 2016; De Vos, Vanvooren, Vanderauwera, Ghesquière, & Wouters, 2017), decreased (Lehongre, Ramus,

Villiermet, Schwartz, & Giraud, 2011), or increased (Lizarazu et al., 2015) in individuals with dyslexia. As for high-gamma oscillations (>40 Hz), increased (Lehongre et al., 2011) or unimpaired (Lizarazu et al., 2015) synchronization is demonstrated. Furthermore, beta synchronization has also proved to be abnormal in dyslexic individuals (De Vos et al., 2017; Poelmans, Luts, Vandermosten, Boets, et al., 2012).

Altogether, it appears that individuals with dyslexia exhibit both delta or theta as well as beta or gamma synchronization deficits. However, to date, it is unknown which of these neural deficits are causally related to the development of dyslexia. An important shortcoming of cross-sectional studies in school-aged children, adolescents, or adults, is that the observed neural deviances might as well reflect the consequential effects of their reading difficulties. To disentangle causal from consequential effects, longitudinal studies following children throughout reading development are indispensable (Goswami, 2015). Yet, there are no preceding studies that have investigated neural processing of speech-related temporal information in relation to reading development.

The objective of the present study was twofold. Our first aim was to elucidate the potential relation between neural processing of speech envelope modulation rates and reading development. We revisited a role for both syllable- and phoneme-level neural processing, since a child's phonological system evolves from awareness of larger phonological units, i.e. syllables, to smaller phonological units, i.e. phonemes, during the first stages of reading acquisition (Ziegler & Goswami, 2005). Secondly, we aimed to determine possible neural markers for deviant phonological sensitivity in children with (a family risk for) dyslexia. To achieve these aims, we longitudinally investigated auditory steady-state responses (ASSRs) in a group of children at the ages of 5, 7, and 9. We specifically measured ASSRs evoked by 4 and 20 Hz modulations to examine neural processing of syllable-rate information (by means of theta oscillations) and phoneme-rate information (by means of beta oscillations), respectively.

2. Materials and methods

An extensive longitudinal study was set up, following a group of children during the first stages of reading development by means of three measurement points. At the age of 5, children had not yet received explicit reading instruction, since formal literacy instruction in Flanders only starts at the age of 6, when a child enters first grade (<http://onderwijs.vlaanderen.be/>). We will therefore refer to this developmental stage as the pre-reading stage. At the ages of 7 and 9, children had respectively received at least one and three years of explicit reading instruction. These developmental stages will further be referred to as the beginning reading stage and the more advanced reading stage. Neurophysiological data collection took place during the summer holidays at the end of the 2nd year of kindergarten, grade 1, and grade 3. A behavioral test battery was subsequently administered at the schools of the children at the start of the 3rd year of kindergarten, grade 2, and grade 4.

2.1. Participants

The original sample consisted of 87 children with bilateral normal hearing, normal non-verbal IQ, and no history of brain injury or neurological disorders (for a detailed description of the original sample, see [Vanvooren, Poelmans, Hofmann, Ghesquière, & Wouters, 2014](#)). Fourteen children decided to discontinue participation in the study, one child was excluded following a diagnosis of general learning difficulties, and EEG measurements of four children were generally unusable because of overall excessive noise levels. Consequently, we were able to retain a longitudinal sample of 68 children for the data presented here.

Based on having at least one first degree relative clinically diagnosed with dyslexia, 32 children were identified as children without a family risk for dyslexia (FRD⁻) and 36 children were classified as children with a family risk for dyslexia (FRD⁺). Retrospective classification of participants as typical (DYS⁻) or dyslexic (DYS⁺) readers was based on two criteria. Children assigned to the DYS⁺ group demonstrated (1) severe and persistent reading problems, implemented as a score below the 10th percentile on the same standardized reading test [i.e. word reading ([Brus & Voeten, 1973](#)) or pseudoword reading ([van den Bos, Spelberg, Scheepstra, & De Vries, 1994](#))] at each measurement point, or (2) severe and persistent spelling problems, implemented as a score below the 10th percentile on a standardized spelling test ([Dudal, 1997](#)) at each measurement point. Because dyslexia is mostly defined as a reading impairment, children fulfilling the second criterion were additionally required to demonstrate reading scores below the 25th percentile at each measurement point. Based on these criteria, 14 children were identified as dyslexic readers, constituting the DYS⁺ group, and 54 children were identified as typical readers, constituting the DYS⁻ group. Demographic data are presented for both FRD⁻ versus FRD⁺ as well as DYS⁻ versus DYS⁺ groups in [Table 1](#). Note that not all data were available for all 68 children: 4 Hz ASSR measurements were unprocessable in two children (1 FRD⁻DYS⁻ and 1 FRD⁺DYS⁻), 20 Hz ASSR measurements were unprocessable in three children (1 FRD⁻DYS⁻, 1 FRD⁺DYS⁻, and 1 FRD⁺DYS⁺), and phonological awareness and RAN tasks were unavailable in two children (1 FRD⁻DYS⁻ and 1 FRD⁺DYS⁺). Consequently, N = 66 for analyzes concerning 4 Hz ASSRs, N = 65 for analyzes

concerning 20 Hz ASSRs, N = 66 for analyzes concerning phonological awareness and RAN, and N = 68 for analyzes concerning reading and spelling.

This study was approved by the Medical Ethical Committee of the University Hospitals of Leuven. Written informed consents were obtained from the parents of all participating children.

2.2. EEG measurements

2.2.1. Recording parameters

EEGs were recorded with the BioSemi ActiveTwo system using 64 active Ag/AgCl electrodes mounted in head caps according to the 10-10 electrode system. Electrode offsets were kept between -30 mV and 30 mV. All recordings were administered in a double-walled soundproof booth with a Faraday cage. The children were asked to lie down on a bed while watching a soundless movie. An experienced test leader was present in the EEG cabin throughout the measurements. For each condition, a 10 min (or 600 sec) EEG recording was collected.

2.2.2. Auditory steady-state responses

ASSRs were evoked by means of auditory stimulation with modulated speech-weighted noise. The carrier noise was adopted from the “Leuven Intelligibility Sentence Test” (LIST; [van Wieringen & Wouters, 2008](#)) and represents the long-term average speech spectrum of 730 sentences of a female speaker. The speech-weighted carrier noise was 100% amplitude modulated at approximately 4 and 20 Hz, to measure synchronization of neural oscillations in the auditory cortex to respectively syllable- and phoneme-rate modulations. Despite the recent interest in dyslexia literature for the representation of stress patterns in speech (~2 Hz), supposedly encoded by delta band oscillations, we were not able to include delta synchronization in this study due to time constraints. To allow comparison with our previous studies in adults ([Poelmans, Luts, Vandermosten, Boets, et al., 2012](#); [Vanvooren, Hofmann, Poelmans, Ghesquière, & Wouters, 2015](#)), all stimuli were presented monaurally at 70 dB SPL through insert earphones to the right ear.

2.2.3. Preprocessing

All preprocessing was done in Matlab R2013a. Each EEG recording was divided into epochs of 1.024 sec, resulting in

Table 1 – Participant characteristics.

		FRD ⁻ (N = 32)	FRD ⁺ (N = 36)	DYS ⁻ (N = 54)	DYS ⁺ (N = 14)
FRD	FRD ⁻ /FRD ⁺			31/23	1/13
DYS	DYS ⁻ /DYS ⁺	31/1	23/13		
Sex	Male/Female	19/13	22/14	35/19	6/8
Handedness ^a	Left/Ambidextrous/Right	0/0/32	5/1/30	3/1/50	2/0/12
Age (in months)	Pre-reading stage	62 (3)	61 (3)	62 (3)	61 (3)
	Beginning reading stage	85 (3)	85 (3)	85 (3)	85 (3)
	Advanced reading stage	109 (4)	109 (3)	109 (4)	109 (3)
Non-verbal IQ ^b		99 (14)	100 (15)	100 (14)	98 (18)

Note. There were no significant differences between groups in terms of sex, age, and non-verbal IQ. Non-right handed children (N = 6) were retained in the sample, since removing these participants did not change the results of the statistical analyzes.

^a Edinburgh Handedness Inventory ([Oldfield, 1971](#)).

^b Standardized scores (mean = 100, SD = 15) on the Wechsler Intelligence Scale for Children—Third Edition (WISC—III—NL): Block Design ([Kort et al., 2005](#); [Wechsler, 1991](#)).

585 epochs per electrode (600 sec/1.024 sec). The amplitude rejection level for artifact rejection was set on an individual basis, until exactly 448 epochs per electrode (77%) were retained. All artifact-free epochs were referenced to electrode Cz and clustered into sweeps of 64 consecutive epochs. This resulted in seven sweeps per electrode (448 epochs/64 epochs), which were subsequently averaged into one sweep per electrode. Next, sweeps were averaged across a pre-selected electrode configuration. Nine electrodes in the left hemisphere (TP7, P1, P3, P5, P7, P9, PO3, PO7, and O1) and nine electrodes in the right hemisphere (TP8, P2, P4, P6, P8, P10, PO4, PO8, and O2) were included, resulting in the construction of two artificial “channels” representing the averaged time signal recorded over the left and right temporo-parieto-occipital hemispheric regions. Our electrode configuration was based on previous research showing that these electrodes are the most sensitive to pick up ASSRs in children (Vanvooren et al., 2014), as well as adults (Vanvooren et al., 2015). A Fast Fourier Transformation (FFT) algorithm was used to convert the time signals of the two artificial channels into a set of complex values that vary with frequency (Fig. 1).

2.2.4. Outcome measures

The ASSR appears in the FFT spectrum as a peak in the frequency bin corresponding to the modulation frequency f . The response amplitude (μV) was defined as $\sqrt{P_f}$, i.e. the root of the power of the Fourier component in frequency bin f . For example, the response amplitude for 4 Hz stimulation was calculated as the root of the power of the Fourier component in the 4 Hz frequency bin. The response amplitude provides a measure for the strength of neural synchronization by reflecting the degree to which neural oscillations synchronize their activity to the modulation frequency.

The fact that activity can be measured in frequency bin f however provides no information about the significance of the response, or in other words, whether the neural oscillations significantly synchronized their activity relative to the stimulus-induced *non-synchronized* background activity. In line with our previous reports (Vanvooren et al., 2015, 2014), the stimulus-induced noise amplitude (μV) was defined as $\sqrt{P_{f \pm 1 \text{ Hz}}}$, i.e. the root of the average power of the Fourier components in an approximately 2 Hz wide frequency band around the modulation frequency (i.e. 60 frequency bins or approximately 1 Hz on each side). For example, the stimulus-induced noise amplitude for 4 Hz stimulation was calculated as the average amplitude in the 3–5 Hz frequency band, excluding the 4 Hz frequency bin.

Before we continued with further data analyzes in terms of response and stimulus-induced noise amplitude, we verified the reliability of our measurements by determining the percentage of participants that exhibited a significant synchronization to the stimulus. Therefore, we calculated the signal-to-noise ratio (SNR), defined as the ratio between the response power P_f and the stimulus-induced noise power $P_{f \pm 1 \text{ Hz}}$. If the $\text{SNR} \geq 4.8 \text{ dB}$, there is a significant difference between P_f and $P_{f \pm 1 \text{ Hz}}$ (F-ratio statistic, $p < .05$; Dobie & Wilson, 1996; John & Picton, 2000), indicating that a reliable ASSR is measured. From Table 2, it can be derived that (1) the mean SNRs are $\geq 4.8 \text{ dB}$ and (2) the percentage of participants with significant responses is $>75\%$, in both hemispheres for all conditions.

2.3. Behavioral measurements

Phonological awareness was assessed by an end-rhyme and end-phoneme identification task at the age of 5 (Vanderauwera, Vandermosten, Dell'Acqua, Wouters, & Ghesquière, 2015), and with a phoneme deletion and spoonerisms task (Boets et al., 2010) at the ages of 7 and 9. A rapid automatized naming (RAN) test (van den Bos, Zijlstra, & Spelberg, 2002) was used to measure non-alphanumeric RAN (subtests Colors and Objects) at the ages of 5, 7, and 9, as well as alphanumeric RAN (subtests Digits and Letters) at the ages of 7 and 9. Literacy skills were evaluated with a word reading test (Brus & Voeten, 1973), a pseudoword reading test (van den Bos et al., 1994), and a writing on dictation test (Dudal, 1997) at the ages of 7 and 9. A summary of the behavioral data is provided for both FRD^- versus FRD^+ as well as DYS^- versus DYS^+ groups in Table 3.

2.4. Statistical analyzes

Statistical analyzes were performed with IBM SPSS Statistics 23.0. The assumption of normality was assessed with a Kolmogorov-Smirnov test. If normality was violated, non-parametric tests were used. Mauchly's test was used to examine the assumption of sphericity and a Greenhouse-Geisser correction was applied if necessary. Levene's test verified that the assumption of homogeneity of variance was not violated. The significance level for exploring assumptions was set at $p < .01$ to adjust for multiple comparisons. For ANOVA post hoc comparisons, the more conservative Bonferroni correction procedure was used. Note that all post hoc comparisons were re-analyzed using paired t-tests for within-subject effects and independent t-tests for between-subject effects to investigate a possible influence of longitudinally missing data on the results. The results of these analyzes will however not be further discussed, since the same results were found as for the ANOVAs. All analyzes were two-tailed ($\alpha = .05$).

3. Results

3.1. Developmental effects

Our first aim was to investigate developmental aspects of syllable- and phoneme-rate auditory processing throughout reading acquisition, regardless of family risk for dyslexia or reading outcome. Therefore, we conducted an FM-ANOVA per EEG condition (4 and 20 Hz ASSRs) and outcome measure (stimulus-induced noise and response amplitudes). Developmental stage (5, 7, and 9 years old) and hemisphere (left and right hemisphere) were included as within-subject variables. In addition, we also investigated correlations between developmental effects in the EEG and behavioral outcome measures.

3.1.1. Stimulus-induced noise amplitudes

For 3–5 Hz noise amplitudes (Fig. 2 (A), dashed lines), a significant main effect of developmental stage ($F_{(2, 117)} = 109.23$, $p < .001$) was found. Overall, children showed a progressive

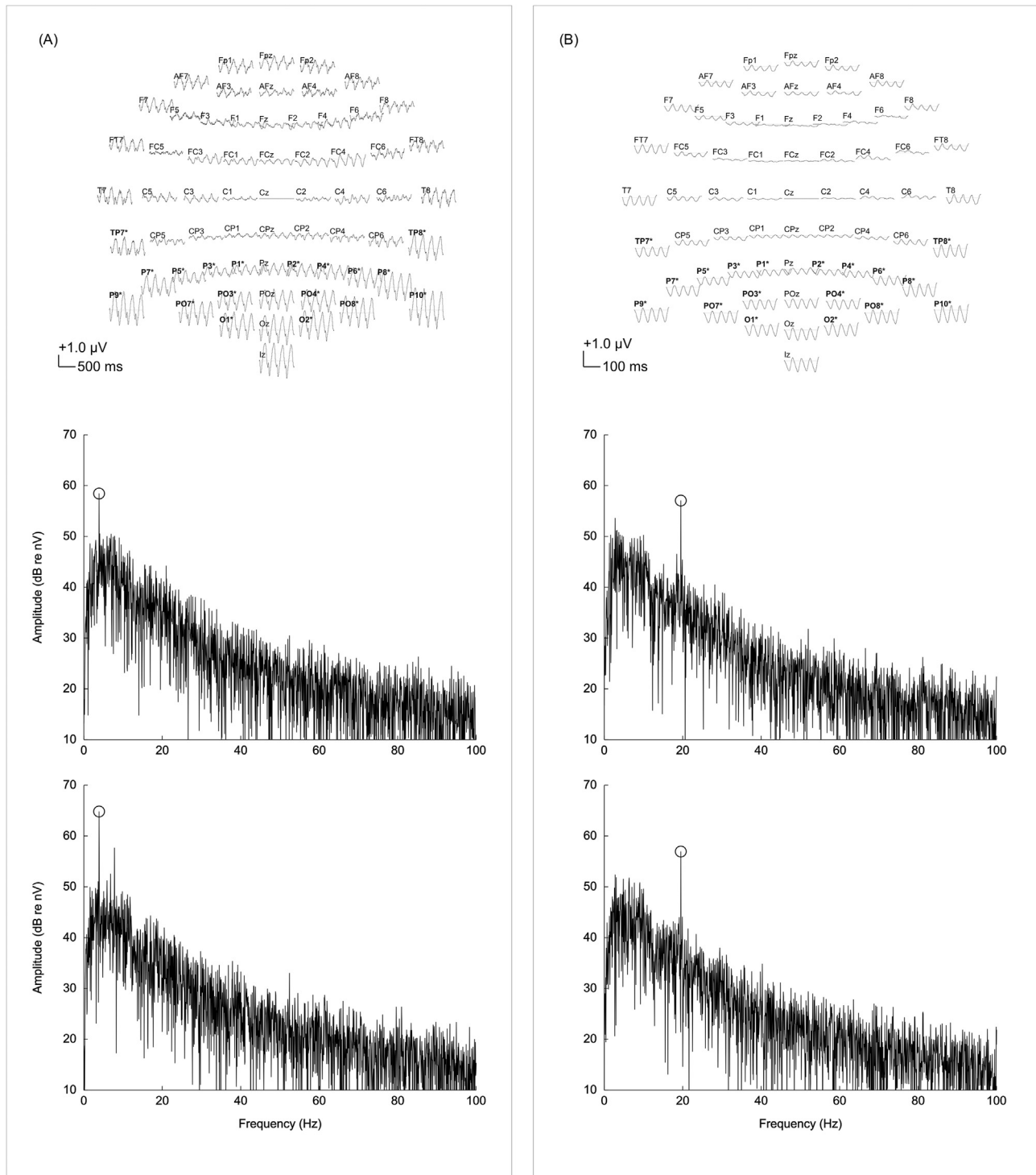


Fig. 1 – Topographic maps and FFT spectra. Panel (A) displays the topographic map and exemplary FFT spectra for left and right hemispheric 4 Hz ASSRs measured at the age of 7. Panel (B) displays the same data for 20 Hz ASSRs. To construct the topographic maps, grand mean averaged response waveforms were created using BESA Research 6.0 software by averaging each recording's 448 artifact-free Cz-referenced epochs over all participants ($N_{4\text{Hz}} = 66$ and $N_{20\text{Hz}} = 65$). The response waveforms are displayed at the approximate electrode locations viewed from the top of the head with the nose at the top of the figure, such that positivity at the electrode location relative to the reference electrode is shown by an upward deflection. By means of these topographic maps, the suitability of our pre-selected electrode configuration (i.e. the electrodes indicated with an asterisk) was verified. The FFT spectra illustrate the resulting raw data for a randomly selected typical reading subject after preprocessing. Note that amplitudes were converted to dB using a logarithmic transformation with reference to 1 nV for graphical reasons.

Table 2 – Mean SNR (dB re μV), corresponding 95% confidence interval, and percentage of participants with significant responses.

		5 years old	7 years old	9 years old
4 Hz	Left hemisphere	8.3 [7.1; 9.5] 76%	9.6 [8.4; 10.8] 80%	10.3 [9.0; 11.7] 82%
	Right hemisphere	10.0 [8.8; 11.2] 85%	11.1 [9.9; 12.2] 91%	12.0 [10.8; 13.3] 89%
20 Hz	Left hemisphere	11.9 [10.4; 13.3] 86%	14.2 [12.9; 15.4] 92%	13.8 [12.5; 15.0] 94%
	Right hemisphere	12.9 [11.5; 14.3] 91%	14.8 [13.5; 16.1] 95%	15.1 [13.9; 16.3] 97%

Note. The number of participants with significant responses did not differ between developmental stages or hemispheres, as investigated by means of paired McNemar tests (all $p > .05$).

decrease in 3–5 Hz noise amplitudes between the ages of 5 and 7 ($MD = .029 \mu\text{V}$, $SE = .005 \mu\text{V}$, $p < .001$), as well as between the ages of 7 and 9 ($MD = .035 \mu\text{V}$, $SE = .004 \mu\text{V}$, $p < .001$). The main effect of hemisphere was not significant ($F_{(1, 65)} = 2.65$, $p = .109$), suggesting no overall hemispheric differences. A significant interaction effect was present between developmental stage and hemisphere ($F_{(2, 130)} = 6.63$, $p = .002$). Post hoc testing confirmed the progressive decrease in 3–5 Hz noise amplitudes in both hemispheres (all $p < .001$), but revealed a specific effect of hemisphere in 7-year-olds, where 3–5 Hz noise amplitudes were significantly larger in the left hemisphere than in the right hemisphere ($MD = .007 \mu\text{V}$, $SE = .002 \mu\text{V}$, $p = .002$).

For 19–21 Hz noise amplitudes (Fig. 2 (B), dashed lines), no main effect of developmental stage ($F_{(2, 128)} = 1.32$, $p = .271$) or hemisphere ($F_{(1, 64)} = .001$, $p = .975$), nor any interaction effect between developmental stage and hemisphere ($F_{(2, 128)} = .25$, $p = .777$) was found.

3.1.2. Response amplitudes

For 4 Hz response amplitudes (Fig. 2 (A), solid lines), a significant main effect of hemisphere ($F_{(1, 65)} = 15.15$, $p < .001$) was found. Overall, 4 Hz response amplitudes were significantly larger in the right hemisphere in comparison to the left hemisphere ($MD = .168 \mu\text{V}$, $SE = .043 \mu\text{V}$). We found no main effect of developmental stage ($F_{(2, 113)} = .34$, $p = .685$), nor any interaction effect between developmental stage and hemisphere ($F_{(2, 102)} = .53$, $p = .548$).

For 20 Hz response amplitudes (Fig. 2 (B), solid lines), a significant main effect of developmental stage ($F_{(2, 100)} = 15.47$, $p < .001$) was found. Overall, children showed a significant increase in 20 Hz response amplitudes during development from age 5 to 7 ($MD = .082 \mu\text{V}$, $SE = .018 \mu\text{V}$, $p < .001$), but not during development from age 7 to 9 ($MD = .017 \mu\text{V}$, $SE = .011 \mu\text{V}$, $p = .342$). A significant main effect of hemisphere ($F_{(1, 64)} = 9.10$, $p = .004$) was also found, demonstrating that 20 Hz response amplitudes were significantly larger in the right hemisphere in comparison to the left hemisphere ($MD = .039 \mu\text{V}$, $SE = .013 \mu\text{V}$). The interaction effect between developmental stage and hemisphere approached significance ($F_{(2, 110)} = 3.03$, $p = .060$), but post hoc testing confirmed the increase in response amplitudes between ages 5 and 7 in both hemispheres (all $p < .001$), as well as the hemispheric effects for 20 Hz response amplitudes in all developmental stages (all $p < .05$).

3.1.3. Correlations with behavioral outcome measures

To obtain a comprehensive measure for the developmental effects observed in the EEG outcome measures, an intra-individual difference score was calculated by subtracting the value of the EEG outcome measure obtained at the age of 5 from the value of the EEG outcome measure obtained at the age of 9. Hence, these individual difference scores represent each child's developmental decrease (in case of a negative value) or developmental increase (in case of a positive value) in stimulus-induced noise or response amplitude between the age of 5 and 9. Subsequently, correlations with behavioral outcome measures of phonological awareness, RAN, and reading were calculated.

For 4 Hz ASSRs, no significant correlations were found between development of neural auditory processing and behavioral outcomes (all $p > .1$; Table 4, top rows), indicating that developmental changes in noise or response amplitude in the theta band were not related to phonology or reading development.

For 20 Hz ASSRs, no significant correlations were found between beta range stimulus-induced noise levels and behavioral outcomes (all $p > .1$), but significant correlations were found between the developmental change of 20 Hz response amplitudes and phonological awareness, alpha-numeric RAN, and reading skills measured at ages 7 and 9 (Table 4, bottom rows). Interestingly, the obtained correlation coefficients demonstrated a negative relation between the developmental change in 20 Hz response amplitudes and behavioral outcomes, indicating that those children who showed the largest developmental increase in 20 Hz response amplitudes throughout reading acquisition eventually develop the poorest phonological and reading skills.

3.2. Family risk effects

Our second aim was to identify possible neural markers for deviant phonological sensitivity in children (with a family risk for) developing dyslexia later on.

First, we investigated group differences specific to the family risk for dyslexia, regardless of reading outcome. Therefore, we conducted the same FM-ANOVA per EEG condition and outcome measure, with the addition of family risk for dyslexia (FRD^- and FRD^+) as between-subject variable. Developmental stage and hemisphere were retained as within-subject variables, to examine whether family risk for

Table 3 – Behavioral outcome measures.

	FRD [−]	FRD ⁺	<i>p</i>	DYS [−]	DYS ⁺	<i>p</i>
5 years old						
<i>Phonological awareness</i>						
End rhyme ^{a,b}	10 (4)	9 (4)	.200	9 (3)	7 (4)	.008
End phoneme	4 (2)	5 (2)	.328	5 (2)	3 (2)	.068
Composite	.0 (.6)	.0 (.9)	.741	.1 (.8)	−.6 (.7)	.003
<i>Non-alphanumeric RAN</i>						
Colors	.7 (.2)	.6 (.1)	.016	.7 (.2)	.5 (.1)	.008
Objects	.6 (.2)	.6 (.2)	.084	.6 (.2)	.5 (.2)	.021
Composite ^b	.3 (1.0)	−.2 (.9)	.028	.0 (.9)	−.5 (.6)	.003
7 years old						
<i>Phonological awareness</i>						
Phoneme deletion ^b	16 (6)	13 (7)	.092	17 (9)	5 (9)	<.001
Spoonerisms	25 (11)	22 (12)	.247	26 (11)	13 (7)	<.001
Composite ^{a,b}	.5 (1.4)	−.3 (1.6)	.132	.5 (1.2)	−1.0 (1.0)	<.001
<i>Non-alphanumeric RAN</i>						
Colors ^a	.9 (.3)	.8 (.3)	.267	.9 (.2)	.8 (.2)	.031
Objects	.9 (.2)	.8 (.2)	.041	.9 (.2)	.8 (.2)	.079
Composite	.2 (1.0)	−.2 (.9)	.054	.1 (.9)	−.5 (.9)	.035
<i>Alphanumeric RAN</i>						
Digits	1.4 (.4)	1.1 (.3)	.011	1.3 (.3)	.9 (.3)	<.001
Letters	1.4 (.3)	1.2 (.3)	.004	1.4 (.3)	1.0 (.2)	<.001
Composite	.3 (.9)	−.3 (.9)	.004	.2 (.8)	−.9 (.7)	<.001
<i>Reading</i>						
Word reading	29 (13)	20 (13)	.006	28 (12)	9 (4)	<.001
Pseudoword reading	22 (9)	16 (11)	.018	22 (9)	7 (3)	<.001
Composite	.3 (.9)	−.3 (1.0)	.009	.3 (.9)	−1.1 (.3)	<.001
Spelling ^a	54 (6)	50 (10)	.043	53 (5)	37 (16)	.003
9 years old						
<i>Phonological awareness</i>						
Phoneme deletion ^{a,b}	24 (6)	22 (9)	.021	24 (4)	15 (9)	<.001
Spoonerisms ^{a,b}	41 (8)	36 (14)	.261	42 (9)	27 (14)	<.001
Composite ^{a,b}	.6 (.9)	.3 (1.6)	.049	.6 (.7)	−1.3 (1.0)	<.001
<i>Non-alphanumeric RAN</i>						
Colors	1.2 (.2)	1.0 (.2)	.012	1.1 (.2)	1.0 (.2)	.068
Objects	1.1 (.2)	1.0 (.2)	.014	1.1 (.2)	.9 (.2)	.050
Composite	.3 (.9)	−.3 (.9)	.009	.1 (1.0)	−.5 (.8)	.047
<i>Alphanumeric RAN</i>						
Digits	2.0 (.4)	1.7 (.4)	.004	1.9 (.4)	1.4 (.3)	<.001
Letters	1.9 (.4)	1.6 (.4)	.005	1.8 (.4)	1.4 (.2)	<.001
Composite	.4 (.9)	−.3 (.8)	.002	.2 (.9)	−1.0 (.4)	<.001
<i>Reading</i>						
Word reading	55 (13)	44 (16)	.003	55 (12)	27 (9)	<.001
Pseudoword reading	45 (14)	31 (16)	<.001	43 (14)	17 (6)	<.001
Composite	.4 (.8)	−.4 (1.0)	.001	.3 (.7)	−1.3 (.4)	<.001
Spelling	44 (10)	35 (12)	.002	43 (9)	26 (10)	<.001

Note. Mean (SD) and *p* values of group differences from independent *t*-tests are provided for normally distributed data, median (interquartile range) and *p* values of group differences (from Mann–Whitney *U*-test) are provided for non-normally distributed data. For phonological awareness, RAN, and reading tasks, raw scores of each subtest were converted to *z* scores and averaged to form a composite score. Note that similar results were obtained when DYS⁺ children were compared to FRD[−]DYS[−] children (i.e. when FRD⁺ children were omitted from the DYS[−] group).

^a Non-normally distributed data within FRD[−] and/or FRD⁺ groups.

^b Non-normally distributed data within DYS[−] and/or DYS⁺ groups.

dyslexia interacted with the previously described developmental effects.

For 3–5 and 19–21 Hz noise amplitudes, as well as for 4 and 20 Hz response amplitudes, no main effects of family risk (all *p* > .1) nor any interaction effects with this factor (all *p* > .1) were found. Note that similar results were obtained when FRD⁺DYS[−] children were compared to FRD[−]DYS[−] children (i.e. when DYS⁺ children were omitted from both groups).

3.3. Reading outcome effects

Next, we investigated group differences specific to reading outcome, regardless of the family risk for dyslexia. Once more, a set of FM-ANOVA were conducted, now entering reading outcome (DYS[−] and DYS⁺) as between-subject variable. Developmental stage and hemisphere were again included as within-subject variables to investigate whether reading

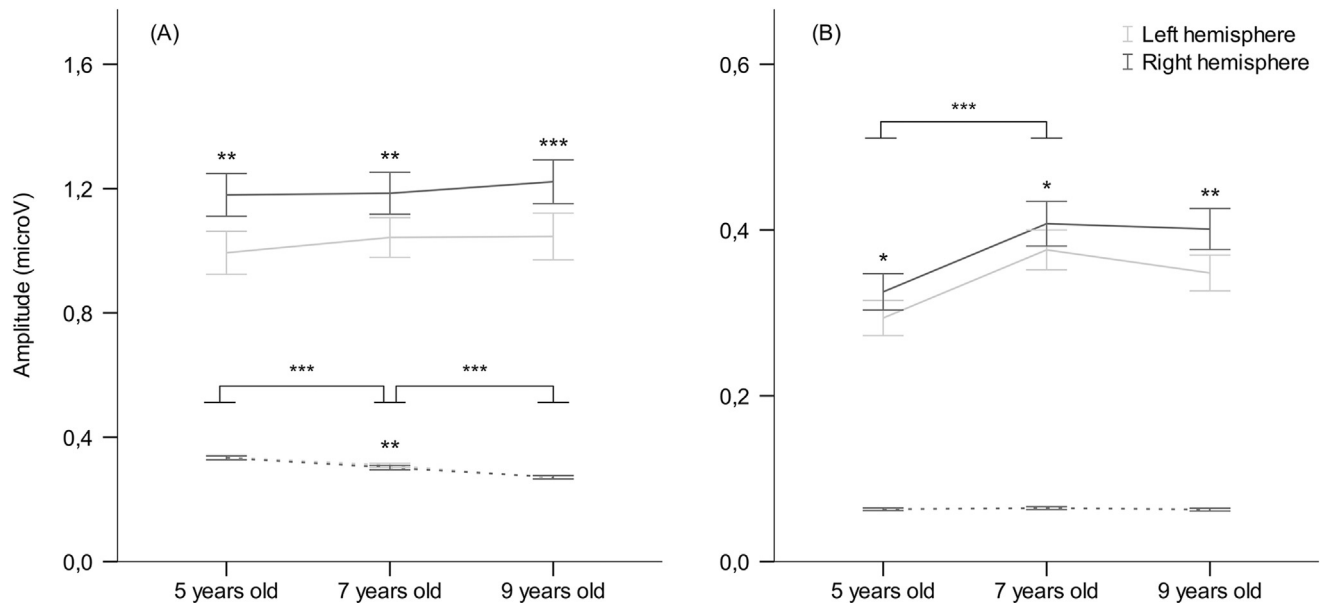


Fig. 2 – Noise and response amplitude differences between developmental stages and hemispheres. Panel (A) represents results for 4 Hz ASSRs, i.e. noise amplitudes between 3–5 Hz (dashed lines) and response amplitudes at 4 Hz (solid lines). Panel (B) represents results for 20 Hz ASSRs, i.e. noise amplitudes between 19–21 Hz (dashed lines) and response amplitudes at 20 Hz (solid lines). Results are displayed separately for left and right hemisphere. Error bars indicate ± 1 SE. Bonferroni corrected two-tailed significances are indicated using * for $p \leq .05$, ** for $p \leq .01$, and *** for $p \leq .001$.

Table 4 – Correlations between developmental aspects in the EEG^a and behavioral outcome measures.

	Phonological awareness		Alphanumeric RAN		Reading	
	7 years old ^b	9 years old ^b	7 years old	9 years old	7 years old ^b	9 years old
4 Hz ASSRs						
<i>Noise amplitude</i>						
Left hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>Response amplitude</i>						
Left hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
20 Hz ASSRs						
<i>Noise amplitude</i>						
Left hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Right hemisphere	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<i>Response amplitude</i>						
Left hemisphere	-.36**	-.26*	-.36**	-.36**	-.39**	-.27*
Right hemisphere	-.31*	-.18	-.42***	-.40**	-.32**	-.29*

Note. Pearson correlation coefficients are provided for normally distributed data, Spearman rho correlation coefficients are provided for not-normally distributed data. *Phonological awareness* represents the composite of the phoneme deletion and spoonerisms tasks. *Alphanumeric RAN* represents the composite of the Digits and Letters RAN subtests. *Reading* represents the composite of the word reading and pseudoword reading tests. Uncorrected two-tailed significances are indicated using * for $p \leq .05$, ** for $p \leq .01$, and *** for $p \leq .001$.

^a It is to be noted that the reported correlations, using individual difference scores of EEG outcome measures, are not confounded by individual differences at the pre-reading stage (since the same results were found when pre-reading noise and response amplitudes were included as a control variable), nor by group differences at the pre-reading stage (since there are no significant pre-reading differences between FRD⁻ versus FRD⁺ nor between DYS⁻ versus DYS⁺ in any of the EEG outcome measures, as further analyzes will show).

^b Non-normally distributed data across groups.

outcome interacted with the previously described developmental effects.

For 3–5 and 19–21 Hz noise amplitudes (Fig. 3, dashed lines), as well as for 4 Hz response amplitudes (Fig. 3 (A), solid lines), no main effects of reading outcome (all $p > .1$), nor any interaction effects with this factor (all $p > .1$) were found.

For 20 Hz response amplitudes (Fig. 3 (B), solid lines), we found a significant main effect of reading outcome ($F_{(1, 63)} = 4.79$, $p = .032$). Overall, DYS⁺ children showed significantly larger 20 Hz response amplitudes in comparison to DYS⁻ children ($MD = .11 \mu V$, $SE = .05 \mu V$). A significant interaction effect between reading outcome and

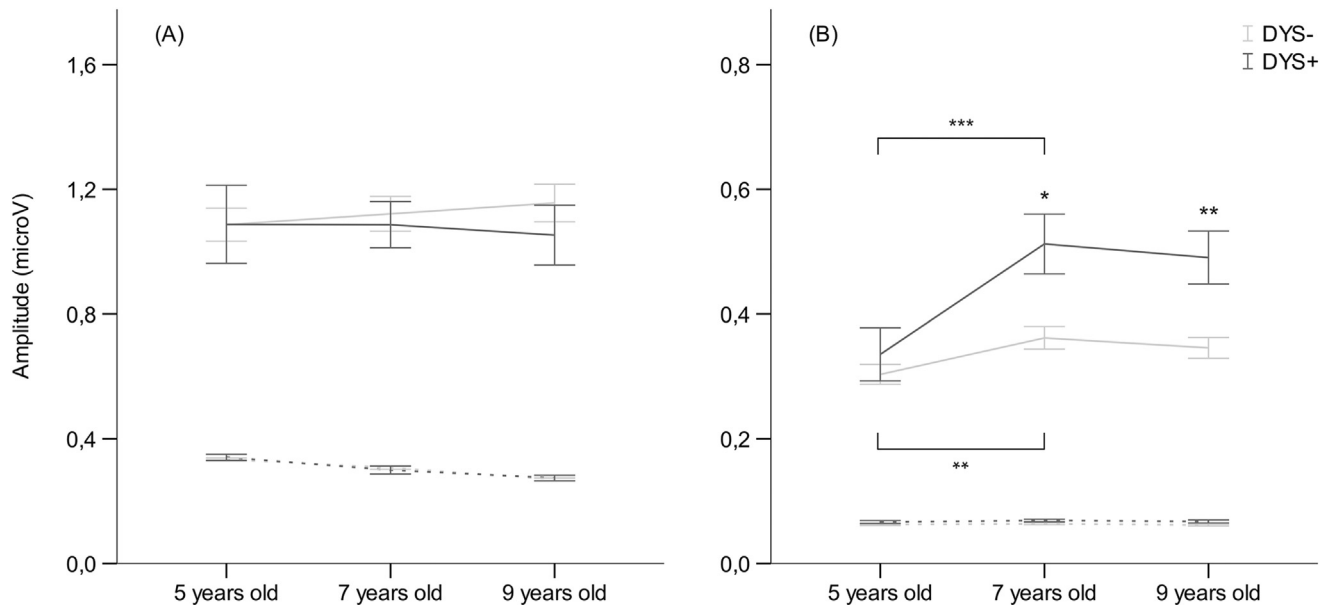


Fig. 3 – Noise and response amplitude differences between DYS⁻ and DYS⁺ groups. Panel (A) represents results for 4 Hz ASSRs, i.e. noise amplitudes between 3–5 Hz (dashed lines) and response amplitudes at 4 Hz (solid lines). Panel (B) represents results for 20 Hz ASSRs, i.e. noise amplitudes between 19–21 Hz (dashed lines) and response amplitudes at 20 Hz (solid lines). Because no significant interactions with hemisphere were found, results are presented averaged over left and right hemisphere. Error bars indicate ± 1 SE. Bonferroni corrected two-tailed significances are indicated using * for $p \leq .05$, ** for $p \leq .01$, and *** for $p \leq .001$.

developmental stage was also found ($F_{(2, 102)} = 6.35$, $p = .005$). Post hoc testing confirmed the developmental increase in 20 Hz response amplitudes from age 5 to 7 in both DYS⁻ and DYS⁺ children (all $p < .01$). However, the group difference between DYS⁻ and DYS⁺ children appeared to be not yet present at the age of 5 ($p = .531$), but emerged only later at the age of 7 ($p = .013$) and was persistent at the age of 9 ($p = .008$). The interaction effect between reading outcome and hemisphere was not significant ($F_{(1, 63)} = 1.28$, $p = .263$). Note that similar results were obtained when DYS⁺ children were compared to FRD⁻DYS⁻ children (i.e. when FRD⁺ children were omitted from the DYS⁻ group).

4. Discussion

Accurate processing of temporal information in speech is crucial for the formation of well-specified phonological representations, which in turn provide the foundation for later reading development. While previous neuro(physio)logical research has mainly focused on experienced readers, little is known about the neural aspects underlying auditory temporal processing during reading development. Therefore, the first objective of the present study was to longitudinally investigate auditory processing of speech-related temporal information throughout the first stages of reading acquisition. Secondly, we aimed to identify if and when deviances in auditory processing emerge in children who develop dyslexia later on.

4.1. Neural processing of syllable-rate information

4.1.1. Theta range neural background activity: Gradual decrease with age

Stimulus-induced noise in the theta range demonstrated a progressive decrease between pre-reading and more advanced reading stages. However, these changes in neural background activity were not related to phonological or reading skills, nor did we find any group differences in neural background activity between children with and without (a family risk for) dyslexia. The latter findings suggest that more general age-related maturational changes, rather than neural changes related to reading acquisition, are underlying the observed developmental effect in neural background activity.

This interpretation is supported by resting-state EEG studies, which have consistently reported gradual decreases in spontaneous slow-wave EEG activity throughout childhood, adolescence, and young adulthood (Barriga-Paulino, Flores, & Gómez, 2011; Clarke, Barry, McCarthy, & Selikowitz, 2001; Cragg et al., 2011; Gmehlin et al., 2011; Rodríguez Martínez et al., 2012; Somsen, Van't Klooster, Van Der Molen, Van Leeuwen, & Licht, 1997). Although the aforementioned studies differ in the specific age ranges that were investigated, Somsen et al. (1997) demonstrated a decrease in slow-wave EEG activity already around the age of 5. Our results are also in agreement with a previous cross-sectional ASSR study by Vanvooren et al. (2015), which demonstrated significantly higher levels of neural background activity in the theta range in normally developing 5-year-old children in comparison to

adults during auditory processing. A similar theta range difference was also found between 3- to 5-year-olds and adults in a recent MEG study (Tang, Brock, & Johnson, 2016).

Since spontaneous slow-wave EEG activity arises from post-synaptic activity of cortical pyramidal neurons, age-related changes in the anatomy of the cortex could provide a plausible explanation for the changing theta range background activity. During childhood and adolescence, the brain exhibits a significant decrease in gray matter (Gogtay et al., 2004; Khundrakpam, Lewis, Zhao, Chouinard-Decorte, & Evans, 2016; Sowell, Thompson, & Toga, 2004), presumably due to selective pruning of synapses that were naturally overproduced earlier in life (Low & Cheng, 2006). If we assume that neural background noise in the theta range at young age indeed reflects the combined activity of necessary and redundant synapses, synaptic pruning might be causally related to the maturational decrease in activity. This hypothesis was investigated and confirmed by Whitford et al. (2007) in adolescents. However, this structural–functional relation has not yet been investigated in young children.

4.1.2. Neural synchronization of theta oscillations: No effects
Our results indicated no developmental changes in neural synchronization to 4 Hz syllable-rate modulations. Neither did we find any correlations with phonology or reading development, nor any group differences related to (a family risk for) dyslexia.

Previous EEG studies examining 4 Hz ASSRs found significantly smaller ASSR amplitudes in adults compared to 5-year-olds (Vanvooren et al., 2015) and school-aged children (Tlumak, Durrant, Delgado, & Boston, 2012), which could be interpreted as evidence for a decrease in neural synchronization to syllable-rate information throughout childhood. However, depending on how ASSR amplitudes are calculated, the finding of smaller 4 Hz response amplitudes in adults might also be a consequence of the age-related decrease in theta range background noise. In these cases an outcome measure that takes the neural background noise into account, e.g., the SNR, might be more appropriate. Indeed, a specific comparison of our 4 Hz SNR values obtained in 5-, 7-, and 9-year-old children (9.2 dB, 10.3 dB, and 11.2 dB respectively) with the 4 Hz SNR values we have obtained in adults (12.3 dB; Vanvooren et al. (2015); derived data provided by the courtesy of dr. Vanvooren), reveals comparable but certainly not smaller 4 Hz SNRs in adults. Accordingly, MEG studies that investigated neural synchronization to syllable rates in terms of phase locking values also found no significant differences between children and adults (Lizarazu et al., 2015; Tang et al., 2016).

Despite the established relevance of 4 Hz modulation rates (Drullman, Festen, & Plomp, 1994a, 1994b; Edwards & Chang, 2013; Greenberg, Carvey, Hitchcock, & Chang, 2003) and oscillatory theta synchronization (Ghitza, 2013; Luo & Poeppel, 2012; Peelle & Davis, 2012) for speech perception, we found no correlations between neural synchronization to syllable-rate modulations and the development of later phonological or reading skills. While we do not seek to question the importance of syllable-rate modulations for speech perception, our results do seem to temper the importance of 4 Hz syllable-rate processing for phonological

and reading development between the ages of 5 and 9. This is consistent with other studies demonstrating normal neural processing of 4 Hz modulations in individuals with developmental dyslexia (Hämäläinen et al., 2012), including our own studies in pre-reading children with a family risk for dyslexia (Vanvooren et al., 2014), dyslexic adolescents (De Vos et al., 2017), and adults (Poelmans, Luts, Vandermosten, Boets, et al., 2012). Together, these findings suggest that an impairment in theta synchronization is unlikely to constitute the underlying cause for deficient syllable-level representations in dyslexia, thereby challenging the framework proposed by Goswami (2011). In this context, ~2 Hz modulation rates (i.e. stressed syllables) and delta oscillations might occupy a more prominent role than initially prevised, given the growing number of studies demonstrating deviant neural delta synchronization in individuals with dyslexia (Cutini et al., 2016; Hämäläinen et al., 2012; Molinaro et al., 2016; Power, Mead, Barnes, & Goswami, 2013; Power et al., 2016; Soltész et al., 2013). These novel insights urge for studies investigating delta synchronization in relation to reading development, in order to elucidate the causal nature of these effects.

4.2. Neural processing of phoneme-rate information

4.2.1. Neural synchronization of beta oscillations: Increase around the onset of reading acquisition

Neural synchronization to 20 Hz phoneme-rate modulations demonstrated a significant increase between pre-reading and beginning reading stages. The increase in neural synchronization to phoneme rates correlated significantly with later phonological and reading skills, indicating that children who exhibited the largest increase in neural synchronization to phoneme rates developed the poorest phonological and reading skills.

While Tlumak et al. (2012) and Vanvooren et al. (2015) found no significant differences in 20 Hz response amplitudes between children and adults, Tlumak et al. (2012) did report considerably (but non-significantly) larger 20 Hz response amplitudes in adults. Further evidence for stronger neural synchronization to phoneme rates in experienced readers compared to pre-readers has been provided in terms of EEG phase coherence (Vanvooren et al., 2015), as well as MEG phase locking values (Tang et al., 2016). Interestingly, comparing our 20 Hz SNR values obtained in 5-, 7-, and 9-year-old children (12.4 dB, 14.5 dB, and 14.4 dB respectively) with the 20 Hz SNR values we have obtained in adults (14.5 dB; Vanvooren et al. (2015); derived data provided by the courtesy of dr. Vanvooren), shows that SNRs in 5-year-olds are indeed substantially lower than in adults, whereas SNRs in 7- and 9-year-olds approach adult-like levels very closely. Hence, our findings suggest that a maturational process is triggered around the onset of reading acquisition, which increases neural synchronization to phoneme-rate modulations from immature pre-reading levels to adult-like levels. As phoneme awareness is thought to develop as a consequence of learning to read (Ziegler and Goswami (2005); however, see also Hulme, Caravolas, Málková, and Brigstocke (2005) for a critical discussion), the remarkable coincidence between the increase in neural synchronization to phoneme-rate modulations and the

onset of reading acquisition, might reflect the emergence of phoneme awareness in beginning readers.

The increase in phoneme-rate synchronization might be attributable to specific experience-driven changes in the auditory cortex. Besides a general age-related decrease in gray matter, MRI studies in children and adolescents also demonstrated an increase in white matter (Lenroot & Giedd, 2006; Paus et al., 2001). Specifically in anatomical pathways supporting auditory processing, white matter development appears to be characterized by an exponential growth curve from the age of 5 (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Hence, myelination and changes in white matter density could be contributing to the increased neural responsiveness of the auditory system to phoneme-rate modulations. An alternative explanation could be the refinement of inhibitory circuits (Cho et al., 2015; Poulsen, Picton, & Paus, 2007, 2009). GABAergic inhibitory neurons are widespread in the auditory cortex and have also been suggested to improve temporal encoding (Hasenstaub et al., 2005).

4.2.2. Emerging phoneme-rate processing deficits in dyslexia Children who developed dyslexia later on showed significantly larger response amplitudes during auditory processing of phoneme-rate modulations in comparison to typically developing children. This atypical synchronization to phoneme rates emerged after one year of reading instruction and was persistent after three years of reading instruction.

These results are in line with our recent findings in dyslexic adolescents, who also demonstrated significantly increased 20 Hz responses in comparison to normal reading adolescents (De Vos et al., 2017). Other studies in school-aged children and adults with dyslexia, suggested similar “oversynchronization” to phoneme-rate modulations, although these effects were rather situated in the gamma frequency range (>40 Hz: Lehongre et al., 2011; 30 Hz: Lizarazu et al., 2015). Together, these findings indicate that children who go on to develop dyslexia exhibit normal phoneme-rate synchronization at a pre-reading age, but develop an atypically high neural responsiveness to phoneme rates around the onset of reading acquisition, which is persistent into adolescence and young adulthood. Because these atypical patterns arise at a later age, they seem to reflect the consequential effects rather than the underlying cause for emerging reading problems in dyslexia. Hence, there is need for a thorough reflection on and revision of the role of phoneme-rate processing in dyslexia.

As discussed above, both developmental increases in white matter as well as refinement of inhibitory circuits, may provide an explanation for the increased neural synchronization to phoneme rates around the onset of reading development. An atypically large increase in neural synchronization could therefore be related to deviant white matter development or immature inhibitory circuits in the dyslexic brain. The latter explanation regarding inhibitory circuits remains to be investigated, but we are willing to speculate about white matter development in relation to beginning reading problems and dyslexia. In the framework of the current longitudinal study, MRI data were intermediately collected in the same group of children at the end of the 3rd year of kindergarten (Vanderauwera et al., 2015; Vandermosten et al., 2015) and at the end of grade 2. The longitudinal MRI results suggest

an atypically large white matter increase in those children who developed dyslexia later on (Vanderauwera, 2016). Interestingly, these findings were specific to the arcuate fasciculus, a white matter tract that anatomically includes auditory regions (Catani & Thiebaut de Schotten, 2008) and has been suggested to be functionally involved in phonological processing during speech perception (e.g., Vandermosten, Price, & Golestani, 2016). Future studies specifically addressing the dynamics of the structural-functional relationship between white matter properties and auditory processing during the first stages of reading acquisition promise to reveal interesting findings.

4.3. A note on hemispheric lateralization of ASSRs

According to the Asymmetric Sampling in Time (AST) model of cortical speech processing (Poeppel, 2003; Poeppel, Idsardi, & van Wassenhove, 2008), the left and right hemisphere have a functional preference to process certain modulation rates. Whereas the right hemisphere is thought to preferentially process syllable-rate modulations, a left hemispheric preference for phoneme-rate modulations is assumed. At first sight, our results appear to be inconsistent with the AST model, as we found an overall right hemispheric processing preference for both syllable- and phoneme-rate modulations. However, there has recently been some discussion on the origin of the hemispheric asymmetries in speech processing. Some researchers have suggested that the presence of a linguistic content, rather than the acoustical temporal aspects of the stimulus, underlies the assumed leftward lateralization (for comprehensive reviews, see McGettigan & Scott, 2012; Scott & McGettigan, 2013). Since our study used unintelligible non-speech stimuli, this might explain why we observed a different lateralization pattern than proposed by the AST model. In conformity, all our previous ASSR studies have consistently found larger 4 and 20 Hz responses in the right compared to the left hemisphere (Poelmans, Luts, Vandermosten, Boets, et al., 2012; Poelmans, Luts, Vandermosten, Ghesquière, & Wouters, 2012; Vanvooren et al., 2015, 2014). Note that none of the interaction effects with hemisphere was significant, indicating that (1) hemispheric effects were not significantly different between developmental stages and FRD or DYS groups, and (2) vice versa, effects of developmental stage and FRD or DYS were not significantly different between hemispheres.

5. Conclusion

By means of a longitudinal study following children with and without (a family risk for) dyslexia from the age of 5 until the age of 9, we demonstrate that (1) the onset of reading development is associated with an increase in neural responsiveness to phoneme-rate modulations, and (2) dyslexic children exhibit atypically high neural synchronization to phoneme rates after one year of reading instruction. We found no developmental effects regarding neural synchronization to syllable-rate modulations, nor any effects of family risk for dyslexia. In sum, our findings suggest that neural synchronization to phoneme rates may yield a marker for emerging

phoneme awareness around the onset of reading acquisition, and even more, for an atypical development of phoneme-rate processing in beginning readers who go on to develop dyslexia. Since no pre-reading differences in neural synchronization to phoneme-rate modulations were found, phoneme-rate processing deficits that have previously been observed in school-aged children, adolescents, and adults with dyslexia appear to reflect the consequential effects of emerging reading problems in dyslexia, rather than the underlying cause.

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